Prescribing trends, utilisation and comparative effectiveness of antidiabetic drug therapies prescribed in UK primary care

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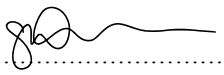
Declarations

I, Samantha Wilkinson, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:  ……..

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Use of published work

Four papers have been published based on work undertaken for this thesis. Work for these papers were carried out as part of the PhD and took place during the period of registration for the PhD. For these papers, Samantha Wilkinson was the lead author, and prepared all protocols and drafts of the papers. The contributions of the co-authors were restricted to providing study advice and comments on the drafts prepared by Samantha Wilkinson.

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Abstract

Background

Over the last decade, several new treatments for type 2 diabetes have launched for routine care in the United Kingdom (UK). Little was known however about how general practitioners (GPs) prescribed these drugs, why GPs chose each therapy, or how they compared in terms of effectiveness.

Methods

This thesis describes prescribing trends and comparative effectiveness of type 2 diabetes drugs, using routine UK clinical care data and observational study designs.

Results

All analyses used a cohort of 280,241 individuals treated in UK primary care between 2000 and 2017. First, I show rapid changes in prescribing practice for type 2 diabetes drugs. After metformin monotherapy, GPs have increasingly added new drug classes, in particular the Dipeptidyl peptidase 4 inhibitors (DPP4is) and sodium glucose cotransporter-2 inhibitors (SGLT2is). From their launch in 2007 and 2012, by 2017 prescriptions for DPP4is and SGLT2is grew to 42% (95% CI: 38, 47) and 22% (95% CI: 17, 27) of therapy intensifications.

To describe patient characteristics associated with treatment intensification with a sulfonylurea (SU), a DPP4i or a SGLT2i, I applied multinomial regression analysis. I found inequalities by socioeconomic status and ethnicity. People of South Asian ethnicity had lower odds of receiving SGLT2is compared to SUs, odds ratio: 0.6 (95% CI: 0.4, 0.9).

Finally, I used a new-user propensity score matched design to contrast intensification with SUs, DPP4is and SGLT2is and reveal differences in clinical variables. People prescribed SGLT2is had the greatest falls in glycated haemoglobin (HbA1c) at 60 weeks, of 16.1 mmol/mol (95% CI: 18.7, 13.5), compared to SUs and DPP4is (13.8 mmol/mol (95% CI: 15.4, 12.2) and 9.8 mmol/mol (95% CI: 11.6, 7.9) respectively).

Conclusions

Electronic health records offer important clinical information for clinicians, and answer questions not investigated by randomised controlled studies. This work addresses methodological challenges in drug research using electronic health records.

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Abbreviations

ACEi	Angiotensin converting enzyme inhibitor
ADA	American Diabetes Association
ARB	Angiotensin 2 receptor blockers
BMI	Body mass index
BP	Blood pressure
CVOT	Cardiovascular Outcome Trials
DPP4is	Dipeptidyl peptidase 4 inhibitors
EASD	European Association for the Study of Diabetes
EMA	European Medicines Agency
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FU	Follow-up
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
HbA1c	Haemoglobin A1c
HF	Heart Failure
HES	Hospital Episodes Statistic
ID	Identification number
IMD	Index of multiple deprivation
MACE	major adverse cardiac events
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
ONS	Office of National Statistics
PPAR-γ	Peroxisome proliferator-activated receptor gamma
RCT	Randomised Controlled Trials
SGLT2is	Sodium-glucose cotransporter-2 inhibitors
SU	Sulfonylureas
TZD	Thiazolidinediones
UK	United Kingdom
US	United States
UTI	Urinary tract infection

1 Chapter 1: Background information and rationale for thesis

Chapter summary

- Type 2 diabetes is a common and increasing global public health burden, characterised by raised blood glucose.
- People with type 2 diabetes are at greater long-term risk for cardiovascular and kidney disease, and mortality.
- Drugs to treat type 2 diabetes show good evidence of reducing blood glucose levels, but evidence is limited for whether drugs reduce long term diabetes-related outcomes.
- Evidence comparing the drugs used to treat diabetes is principally based on clinical trials. However, these studies are restricted in scope and may not be generalisable to primary care settings.
- In this thesis I describe the application of pharmacoepidemiological methods to electronic health records to assess the real-world use of new type 2 diabetes drugs and the comparative effect of these drugs on clinical variables which complements data from clinical trials.

1.1 Type 2 diabetes and long term outcomes

Diabetes is a group of metabolic diseases, characterised by dysregulation and chronic elevation of blood glucose, with a number of subtypes. Type 1 diabetes is an autoimmune disease that results in loss of the insulin-producing β-cell in the pancreas and is predominantly diagnosed in children and young people. Type 2 diabetes is more common, accounting for 75-85% of people with diabetes. Affected individuals show decreased sensitivity to insulin (insulin resistance) and/or decreased secretion of insulin resulting in high blood glucose levels.(2, 3) The pathogenesis of type 2 diabetes is complex and not completely understood, but is likely caused by both environmental, lifestyle and genetic factors.(4)

Prevalence of diabetes in 2015 (encompassing all types of diabetes) was estimated to be 8.8% of the global population, but this is expected to rise to 10.4% by 2040.(5) By 2030, global prevalence of type 2 diabetes is expected to be over 500 million.(6)

People living with type 2 diabetes carry an increased burden of risk for many health problems, including cardiovascular disease, blindness, kidney disease, and nerve damage.(7) They have double the risk of mortality from cardiovascular disease than people without diabetes.(8) Cardiovascular disease is the leading cause of death among people with type 2 diabetes, around 50% of people with type 2 diabetes die from cardiovascular causes.(9, 10) In the UK, diabetic retinopathy is the main cause of blindness and around 30% of people with type 2 diabetes have diabetic retinopathy.(11) Up to 30% of people with diabetes have chronic kidney disease (CKD), compared to 6-

9% in the general population.(12) Global deaths due to type 2 diabetes related kidney disease were estimated to account for 349,000 deaths in 2017.(13)

1.2 Treatment for type 2 diabetes

The aim of type 2 diabetes treatment is to reduce blood glucose and associated adverse health events.(4) **Table 1.1** summarizes the drug classes approved for type 2 diabetes in the UK with their actions, risks and benefits. New drugs must have proven efficacy to lower blood glucose before regulatory agencies will grant a marketing authorisation.(14, 15) However, clinicians are keen to prescribe their patients drugs that provide advantages beyond controlling blood glucose. They want to decrease risks for comorbidities associated with type 2 diabetes such as cardiovascular disease. Blood glucose levels may predict long-term microvascular outcomes such as kidney disease or blindness.(16) Evidence of cardiovascular benefit is less clear.

Drug class	Drug names	Actions	Potential advantages	Concerns
Biguanides	metformin	Decreased liver glucose production, other actions still unclear	Decreased risk CVD.	Risk of lactic acidosis, gastrointestinal side effects, contraindicated eGFR<30 ml/min/1.73 m^2
Thiazolidinediones (TZD)	rosiglitazone, pioglitazone	Increased insulin sensitivity via nuclear transcription factor PPAR-γ	No hypoglycaemias, low-cost generic available	Increased weight gain, bone fractures, sodium retention, oedema and increased risk of heart failure
DPP4 Inhibitors 'gliptins'	sitagliptin, linagliptin, saxagliptin, alogliptin, vildagliptin	Increases concentrations of the incretins GLP1 and GIP. Increases insulin secretion and decreases glucagon secretion	Weight neutral, low risk of hypos. Can be used with reduced renal function	High cost, skin complaints, pancreatitis concerns
Meglitinides	repaglinide, nateglinide	Increases insulin secretion from β-cells	Blunts glucose rises after meals	Hypoglycaemia risk, weight gain
Sulfonylureas (SU)	gliclazide, glimepiride, glipizide	Increases insulin secretion from β-cells	Decreased risk microvascular disease	Hypoglycaemia risk, weight gain
Alpha-Glucosidase Inhibitor	acarbose, miglitol	Reduces absorption of glucose in small intestine	Blunts glucose rises after meals	Gastrointestinal side effects, small effects on HbA1c
GLP1-1 receptor agonist	exenatide, liraglutide, albiglutide, lixisenatide	Increases insulin secretion, and decreases glucagon secretion and gastric emptying	Shown to be effective for weight loss, low risk of hypoglycaemic events.	High cost, gastrointestinal side effects, increases heart rate, pancreatitis concerns, potential to induce thyroid tumours, warnings for renal impairment
Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2is, gliflozins)	canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Inhibit SGLT2 in proximal nephron of the kidney. Reduces glucose reabsorption and increases urinary excretion	Maintain efficacy later in disease. Weight loss, lowering of blood pressure.	High cost, new drug class. Requires good renal function. Increased genital mycotic infections and UTIs. Volume depletion

References: (17-19, 20)

Table 1.1 List of oral type 2 diabetes drugs available in the UK with descriptions of their actions and perceived risks and benefits

Abbreviations: CVD: Cardiovascular disease, eGFR: estimated glomerular filtration rate, TZD: Thiazolidinediones, PPAR-γ: Peroxisome proliferator-activated receptor gamma, DPP4is: Dipeptidyl peptidase 4 inhibitors, GLP1: Glucagon-like peptide-1, GIP: Glucose-dependent insulinotropic polypeptide, SU: Sulfonylureas, HbA1c: Haemoglobin A1c, SGLT2is: Sodium-glucose cotransporter-2 inhibitors, UTI: Urinary tract infection

1.2.1 Biguanides

The biguanides include metformin, phenformin and buformin. Metformin and phenformin have been used to treat diabetes in the UK since the 1950s. Phenformin and buformin were shown to cause lactic acidosis and are no longer used.(21) Since 2002, the National Institute for Health and Care Excellence (NICE) has recommended metformin as the first line treatment for type 2 diabetes. This was a move away from sulfonylureas as studies indicated that metformin was as effectiveness for reducing blood glucose, and did not lead to weight gains associated with sulfonylureas.(22) Metformin is an insulin-sensitizing agent and works by reducing gluconeogenesis in the liver, a process that is often upregulated among people with type 2 diabetes. It also increases insulin sensitivity in peripheral tissues.(23)

1.2.2 Sulfonylureas

Sulfonylureas have the longest history for the treatment of type 2 diabetes.(24) The class includes older agents (tolbutamide, chlorpropamide, tolazamide and acetohexamide) and newer agents that are more effective (gliclazide, glimepiride, glipizide, glibenclamide, and gliquidone).(25) They were the first class of oral antidiabetic drugs used in clinical practice. Now they are more often used to intensify treatment following the failure of metformin monotherapy. Sulfonylureas lower blood glucose by stimulating insulin secretion in the pancreas. Due to this direct effect on insulin secretion, sulfonylureas are associated with higher risks of hypoglycaemic episodes.(26)

1.2.3 Thiazolidinediones

Thiazolidinediones (TZD) are a class of insulin sensitizers that decrease blood glucose by activating the peroxisome proliferator-activated receptors (PPARs).(27) However, the PPARs have wide-ranging effects on the body and TZDs have a history of adverse effects. The first agent, troglitazone was introduced to the UK in 1997, but then withdrawn following reports of liver toxicity.(28) Rosiglitazone was granted approval in 2000 and prescribed widely, however, in 2010 the European Medicine Agency (EMA) and the United States (US) Food and Drug Administration (FDA) halted marketing authorisation after researchers showed that rosiglitazone was associated with adverse cardiovascular effects.(29, 30) The only TZD available in the UK without restriction is pioglitazone. Yet, the UK Medicines and Healthcare products Regulatory Agency (MHRA) has warned of an association with increased bladder cancer risk, and France recently suspended authorisation for pioglitazone.(31, 32) In 2008, partly in response to the problems with rosiglitazone, the FDA issued new guidance. They now require drug manufacturers to investigate the cardiovascular risk profiles for type 2 diabetes drugs in phase IV post-marketing studies.(33)

1.2.4 Glucagon-like peptide-1 receptor agonists

In 2005, another class of agents was introduced with a different molecular target, the Glucagon-like peptide-1 receptor agonists (GLP1s). These are delivered subcutaneously and bind with the GLP-1 receptors in the β-cells of the pancreas to increase insulin secretion.(34) This class includes the following agents: exenatide, liraglutude, lixisenatide, albiglutide and dulaglutide.(35) The first agent approved in Europe was exenatide in 2006.(36)

1.2.5 Dipeptidyl peptidase 4 inhibitors

Following the success of the GLP-1s, drug companies developed another class of drugs with a similar molecular target, the Dipeptidyl peptidase 4 inhibitors (DPP4is). The DPP4is also exert their action on GLP-1, but instead of acting directly on the receptor, they inhibit the enzyme dipeptidyl peptidase (DPP-4) which cleaves GLP-1.(37) The first agent approved by the European Medicines Agency was sitigliptin in March 2007, followed by vildagliptin later in the same year.(38) The GLP-1s and DPP4is are collectively referred to as the 'incretin mimetics'.

1.2.6 Sodium-glucose cotransporter-2 inhibitors

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) are the newest class of antidiabetic drugs, introduced at the end of 2013. This class inhibits glucose resorption from urine in the kidneys by inhibiting the SGLT2 protein, thus reducing blood glucose levels. The SGLT2i class includes many agents, including: dapagliflozin, empagliflozin, canagliflozin and ertugliflozin.(39)

1.2.7 Other drug classes

General practitioners (GPs) can prescribe other drugs to treat type 2 diabetes, including insulin, alpha-glucosidase inhibitors, and meglinitides. Whilst insulin is an important and widely used medicine for type 2 diabetes, NICE predominantly recommends it for later in therapy. As I focus on early stages of treatment, insulin is out of scope for this thesis. Though NICE-approved, GPs rarely give alpha-glucosidase inhibitors and meglinitides in the UK.(18, 19)

1.3 Treatment guidance

NICE is the body in the UK responsible for reviewing and creating evidence-based guidelines for National Health Service (NHS) providers. At the end of 2015, NICE published an updated set of type 2 diabetes guidelines, which provided a clear prescribing pathway for GPs and included new drug classes. According to these most recent recommendations, before medication, GPs should advise on diet and exercise to help people reduce body weight.(40) Where this is unsuccessful, NICE recommends pharmacotherapy.(40) First-line therapy is metformin unless there are contraindications such as chronic kidney disease.(19, 40) If metformin monotherapy does not adequately control blood glucose, further drugs are added. With the introduction of DPP4is and SGLT2is as treatment options, clinicians in the UK had a wider array of therapies to choose from when prescribing at the first stage of treatment intensification, **Figure 1.1**.

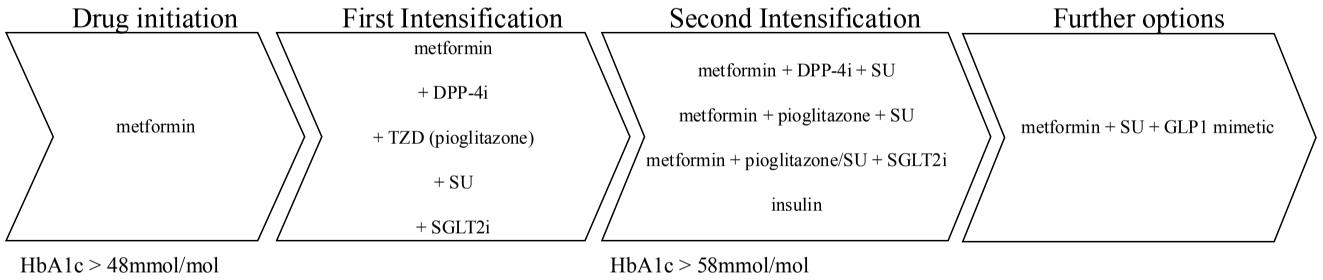

Figure 1.1 Stages of type 2 diabetes drug treatment, and HbA1c targets, as recommended by NICE 2015 guidelines.

Abbreviations: DPP4i: Dipeptidyl peptidase-4 inhibitors, TZD: Thiazolidinediones, SU: Sulfonylureas, SGLT2is: Sodium-glucose co-transporter-2 inhibitors, GLP1: Glucagon-like peptide-1 SGLT2is at first stage of intensification if SU contraindicated.(18)*

According to the 2015 NICE recommendations, clinicians should choose from four drug classes to combine with metformin at the first stage of intensification; DPP4is, SUs, TZDs and SGLT2is.(40) Other international bodies produce guidance for the treatment of diabetes, including the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the Scottish Intercollegiate Guidelines Network (SIGN).

A joint position statement from the ADA and EASD recommend a wider choice of second line intensification agents, and include insulin and GLP-1 receptor agonists as possible additions in metformin therapy in their treatment algorithm.(2, 41) Whereas the Scottish guidelines recommend the same first-stage intensification therapies as the NICE guidance.(42)

1.4 Evidence for new oral drugs:

I embarked on this PhD in late 2015 and formed the plan for the work at the start of 2016. Over the course of my studies, a lot of evidence has emerged about the new oral type 2 diabetes drugs. Some of the most recent evidence is pertinent to the evaluation of the final analysis of this thesis. Therefore, I have provided a brief summary of the evidence to provide context.

1.4.1 Randomised controlled trials (RCTs)

Prior to 2008, the FDA regulatory frameworks for introducing new diabetes treatments required drug companies to show non-inferiority of new agents against placebo and active comparators for reducing blood glucose. These studies were, in the main, of short duration and so did not address long-term changes in outcomes that are important for people with diabetes, such as cardiovascular and kidney disease.(43)

Analysis of the UK Prospective Diabetes Study (UKPDS) data demonstrated that lower glycated haemaglobin (HbA1c) led to decreased risks of mortality and microvascular disease: a 1% decrease in HbA1c was associated with 21% reduced risk of death, 37% reduced risk of microvascular disease and 14% reduction of risk for myocardial infarction.(44) However, the benefits of lowering HbA1c on risk for macrovascular complications remains unclear. Subsequent studies that compared standard to intensive blood glucose control, including ADVANCE, ACCORD, VADT, and a meta-analysis found heterogeity in the effect of intensive glucose reductions on cardiovascular outcomes.(9, 45-47) These studies indicated that intensive glucose lowering did not lead to benefits in cardiovascular mortality, and may

be associated with poorer cardiovascular outcomes for some individuals.(48, 49) These studies did not make comparisons between drugs, but between HbA1c targets, and used a range of drugs to achieve HbA1c control including metformin, TZDs and SUs.

Post-marketing studies of cardiovascular outcomes

In 2008, the FDA issued guidance, to require drug companies to investigate cardiovascular outcomes for type 2 diabetes drugs once licensed.(33) As a result, a number of cardiovascular outcome studies were initiated, summarised in **Table 1.2**.

Year	Study name	Summary	Study size, FU	Key findings
DPP4 inhibitors				
2013	Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE) (50)	The alogliptin versus placebo with standard care for people with type 2 diabetes and Acute Coronary Syndrome (ACS) for the composite outcome MACE	5,380, median 17.5 months	Similar rates of MACE compared to placebo for Alogliptin compared to placebo.
2015	Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (51)	Usual care plus sitagliptin in people with type 2 diabetes and CV disease, for CV death, MI, stroke or hospitalisation of angina.	14,671, median 3 yrs.	No evidence of increased CVD with sitagliptin compared to placebo.
2017	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 Trial (SAVOR-TMI 53) (52)	Compare saxagliptin to placebo for diabetic nephropathy among people with high CV risk	16,492, median 2.1 yrs.	Treatment group associated with improved or less deterioration of ACR.
2019	Cardiovascular safety and Renal Microvascular outcome study with Linagliptin (CARMELINA) (53)	Linagliptin vs. placebo in people with type 2 diabetes and increased CV or kidney disease for CV mortality, MI or stroke, and end-stage kidney disease, decrease in eGFR (≥40% decrease)	6,980	No longer recruiting (NCT01897532)
SGLT2 inhibitors				
2015	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients.(EMPA-REG OUTCOME) (54)	Compare empagliflozin to placebo for composite outcome of cardiovascular death, MI, stroke.	7,020, median 3.1 yrs.	Lower CV mortality for SGLT2is. Higher AE rates for genital infection SGLT2i.

Year	Study name	Summary	Study size, FU	Key findings
2017	Canagliflozin and Cardiovascular Events in Type 2 Diabetes (CANVAS) (55)	Compare canagliflozin to placebo among people with type 2 diabetes and high cardiovascular risk for a composite of cardiovascular death, MI, or stroke.	10,142, median 3.62 yrs.	Lower CV mortality rates in treatment group. Possible benefits for renal function.
2019	Effects of Dapagliflozin on the Incidence of Cardiovascular Events: DECLARE-TIMI 58 (56)	Compare dapagliflozin to placebo in people with CV disease and CV disease risk factors, for outcomes MACE and CV mortality or hospitalisation for HF. Decrease in eGFR by 40%, or more.	17,160, median 4.2 yrs.	Lower heart failure hosp. and CV mortality. Slower renal decline and fewer renal deaths.
2019	Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) (57)	Canagliflozin, vs. placebo among people with type 2 diabetes and kidney disease for composite of end-stage renal disease, doubling of creatinine, renal or CV death.	4,464	Canagliflozin reduced composite renal outcome compared to placebo (hazard ratio, 0.66; 95% CI, 0.53-0.81).
2020	A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (DAPA-CKD) (58)	Dapagliflozin, to placebo in people with type 2 diabetes and kidney disease for composite of end-stage renal disease, eGFR decline (≥50%), renal or CV death.	4,000	Currently recruiting (NCT03036150)

Table 1.2 Timeline and summary of notable placebo-controlled clinical trials for oral antidiabetic drugs for diabetes, cardiovascular, heart failure and renal outcomes.

Abbreviations: CI: confidence interval, CVD: Cardiovascular disease, MACE: major adverse cardiac events, MI: Myocardial infarction, HF: Heart Failure, FU: Follow-up

Some studies, including CANVAS, EMPA-REG, DECLARE-TIMI and CREDENCE have demonstrated cardiovascular benefits for the SGLT2i class of agents, and are shaping guidance.(43) The most recent 2018 ADA-EASD position statement now recommends prescribing of SGLT2is or GLP-1s to people with increased cardiovascular disease risk at treatment intensification following metformin monotherapy.(41)

The trials also identified SGLT2is as potential modifiers of renal outcomes. The CREDENCE study investigated the SGLT2i canagliflozin in people with kidney disease, and found that, compared to placebo, the canagliflozin treated group had a 34% (95% confidence interval [CI]: 19, 47) reduced risk for a renal-specific composite endpoint (end-stage kidney disease, doubling of creatinine, or death from renal cause).(57) Evidence is growing that the SGLT2i class may be a promising treatment for Diabetic Kidney Disease. Two trials, the ongoing DAPA-CKD and EMPA-KIDNEY will investigate the possible protective characteristics of dapagliflozin and empagliflozin on the kidney.(59)

Three large placebo-controlled studies, TECOS, SAVOR and CARMELINA have investigated the DPP4i class (sitagliptin, saxagliptin and linagliptin respectively). These studies were also completed in limited populations; all recruited people with high risk for, or existing cardiovascular disease. The CARMELINA trial also included people with kidney disease. This class however has not shown the cardiovascular outcome benefits apparent in the SGLT2i class.(60)

The clinical trial evidence is rapidly evolving. Many studies were released over the period of this PhD, and a number of studies are expected to release results in the coming year, such as VERTIS-CV.(61)

However, there are some limitations of the clinical trial evidence and their relevance to type 2 diabetes treatment in routine care:

1. The cardiovascular outcome trials were restricted to people with an increased risk of, or already diagnosed, cardiovascular disease. Therefore, the generalisability of these findings to the population being treated in primary care may be limited.

2. The studies are only of monotherapy treatment regimes, or with a range of background therapies, which is not reflective of the current recommendations for their use. Current NICE recommendations advise their use only in combination with metformin and after metformin alone has failed.

3. Current studies are also predominately placebo-controlled and so the benefits of the active agents compared to other drugs are not yet established.

1.4.2 Comparative evidence for SUs, DPP4is and SGLT2is

For the period investigated, NICE directed clinicians to choose from SUs, TZDs, DPP4is or SGLT2is to add to metformin monotherapy. At the commencement of this work, in 2016, a systematic review summarised the comparative effectiveness evidence for antidiabetic treatments. In their evidence synthesis, they included 204 studies, 165 RCTs and 39 observational studies.(62) Most of the studies found were short-term, with a low number of outcomes reported for the major endpoints.(62) Evidence was limited

for the SGLT2i and DPP4is. They did find that SGLT2is with metformin resulted in a weight loss when compared to combination therapy of metformin with DPP4is.(62) Since this review, and over the course of my studies further comparative studies have been published, summarised below.

1.4.3 Comparative RCTs

A clinical trial, the CANTATA-SU study, compared an SGLT2i to an SU for kidney outcomes. CANTATA-SU found that those randomised to canagliflozin had lower risks for the outcome (30% decline in estimated Glomerular Filtration Rates (eGFR) at 104 weeks), though the confidence interval was wide and did not exclude one (Hazard ratio: 0.66, 95% CI: 0.42, 1.04).(63) Two clinical trials, CAROLINA and GRADE are in progress. CAROLINA is assessing linagliptin against the SU glimepiride for cardiovascular outcomes.(61) GRADE is a pragmatic clinical trial comparing metformin combined with SUs, DPP4is, GLP-1s and insulin for cardiovascular outcomes.(64)

In 2019, a meta-analysis of 14 placebo-controlled studies (including five SGLT2i and four DPP4i comparisons to placebo) showed that SGLT2is reduced incidence of cardiovascular disease, all-cause mortality and renal events compared to DPP4is or GLP1s.(65) Another 2019 network meta-analysis included 91 studies and made pair-wise contrasts across antidiabetic medications. It showed SGLT2is decreased risks for heart failure relative to DPP4is (OR: 0.68, 95% CI: 0.59, 0.78), but the evidence was weaker for comparisons with SUs (OR: 0.70, 95% CI: 0.44, 1.11).(66)

1.4.4 Comparative observational evidence

A review published in 2018 summarised the evidence for SGLT2is and cardiovascular outcomes from nine observational studies.(67) The nine studies made a range of comparisons. Four compared SGLT2i users to non-users.(68-71) Two of the studies compared SGLT2i agents to the DPP4i class (72, 73), one compared an SGLT2i agent to insulin (74) and another two compared specific SGLT2i agents, dapagliflozin and canagliflozin, to users of other agents.(75, 76) The findings strongly favoured SGLT2is for death and cardiovascular outcomes. All-cause mortality was up to 50% lower for SGLT2is than comparator groups.

This review and an editorial from Suissa in 2018 highlighted that these investigations were likely to be limited by flaws in study design and showed significant potential for estimates being biased.(67, 77) The sources of bias highlighted were: i) channelling of new drugs (SGLT2is) to healthier populations, ii) introduction of 'immortal-time' bias, and, iii) a bias referred to by the authors as 'time-lag bias', where studies compared drugs prescribed at different stages of drug intensification.(67, 77) The impact of these sources of bias could lead to overestimations of the clinical benefit of SGLT2is compared to other drugs used in clinical practice.

Further observational studies have made direct comparisons between the second-line therapies SUs, DPP4is and SGLT2is.(78, 79) One used a new-user cohort after metformin monotherapy, and measured changes in HbA1c and weight. They compared people intensifying metformin monotherapy with SGLT2is to DPP4is, SUs and other drugs.(78) However, they did not adjust for important differences between drug cohorts at baseline which may be associated with the outcome. For example, the people

intensified using SGLT2i were younger (55 yrs., standard deviation [SD]: 10.14) than those intensified on DPP4is (60.8 yrs., SD: 12.34) and SUs (61.5 yrs., SD: 12.97).(78)

An observational study of new-users of SUs, DPP4is and TZDs after metformin therapy was published in 2018. The study combined data from multiple cohorts from eight sites and compared rates at which people met HbA1c targets, with secondary outcomes including kidney disorders. This study did not find differences in HbA1c or kidney outcomes between SUs and DPP4i, yet noted distinct heterogeneity in the estimates from the multiple sites included in the analysis.(80)

Whilst the comparative evidence has gained pace over the course of my PhD research, it is still lacking in the following areas:

1. Few head-to-head comparisons of the three drugs currently used in clinical practice to intensify metformin monotherapy (SGLT2is, SU and DPP4is).

2. Improper methodological design or lack of adjustment for baseline characteristics in non-randomised studies.

1.5 Pharmacoepidemiology

Pharmacoepidemiology is a specialism of epidemiology combining the study of clinical epidemiology and pharmacology. Pharmacoepidemiology is becoming increasingly important to the pharmaceutical industry and regulatory agencies.(81) Regulatory bodies regard RCTs as the 'gold standard' for drug studies, where randomisation minimises bias in causal effect estimates. Results from clinical trials form the basis for drug approvals for many international organisations.(33, 81)

However, RCTs have limitations:

i) Can under-represent parts of the target population, for example, people from minority ethnicity groups or individuals of older age.

ii) Are often expensive to conduct and need large sample sizes with long follow-up to determine differences in relevant outcomes.(82)

Developing epidemiological methods, growing availability of routinely collected longitudinal health data, and high costs for clinical trials mean that pharmacoepidemiological research has become more prominent in the regulatory drug world.(81) Such studies offer evidence from routinely collected health records to show the effects of medicines used in clinical practice over the long-term. They can generate evidence for drugs on the market, in broad populations, and for rare outcomes.(83) However, observational studies are susceptible to bias if treated individuals differ systematically to untreated people, detailed in **Section 1.4**.(77, 84, 85)

For antidiabetic therapy, trials undertaken to demonstrate efficacy for reducing HbA1c can be short and include modest numbers of participants to fulfil initial

regulatory requirements. The new requirement to examine cardiovascular outcomes means that studies need many more people, with longer follow-up, and with inclusion criteria restricted to people with high-risks for adverse events to find clinically important differences.

Observational research may fill gaps in the current evidence, by looking at long-term changes in diabetes-related outcomes, whilst making head-to-head comparisons of the drug options. This thesis uses routinely collected data and pharmacoepidemiological methods to complement the growing body of evidence for first-stage intensification antidiabetic treatments.

1.6 Rationale, aims and objectives for project

1.6.1 Aim

The aim of this thesis is to use observational data from UK primary care health records to investigate changing prescribing of oral antidiabetic drugs at the first stage of treatment intensification, and to develop methods to compare these drugs for important clinical outcomes.

1.6.2 Thesis rationale

The results generated from this thesis should help to inform clinical prescribing decisions in UK primary care. It will show the potential of the use of electronic health records to contribute to the comparative effectiveness evidence of type 2 diabetes treatments.

1.6.3 Objectives

The specific objectives of this research are:

- Complete a systematic review of the literature for the comparative evidence for type 2 diabetes drug recommended at the first stage of treatment intensification, with the specific aim of comparing kidney outcomes.

- Determine the frequency and proportions of agents prescribed in UK primary care, and how this changed since 2000 by focusing on the drugs used at both treatment initiation and at initial intensification following metformin monotherapy,.

- Investigate associations between patient characteristics or other attributes and the prescribing practice of primary care physicians.

- Develop methods to contrast multiple treatments using electronic health records and compare type 2 diabetes clinical variables for commonly used oral antidiabetic drugs.

1.7 Thesis arrangement

This thesis is arranged in a research paper style format. I have drafted four manuscripts based on this work, three of which are published in peer-reviewed journals. The final paper is under review. Below summarises each chapter:

Chapter 2: A published systematic literature review of observational and interventional research that compares the effect of oral type 2 diabetes drug regimens on kidney outcomes.

Chapter 3: Describes the methods applied throughout the thesis for data analysis. This section outlines the data sources used, and how treatments were defined using electronic health records.

Chapter 4: Includes a published paper with the results of the first analysis that shows prescribing trends for antidiabetic therapies in the UK. This work presents trends at the first stages of treatment and in the context of contraindications, specifically reduced kidney function.

Chapter 5: Comprises another paper published with Clinical Epidemiology, that describes the patient-level factors associated with prescriptions of first-stage intensification drugs in the routine clinical care of patients with type 2 diabetes.

Chapter 6: Consists of a manuscript that applies propensity score matching to compare changes in clinical variables between the commonly prescribed drugs. This is under review at the British Medical Journal (BMJ).

Chapter 7: First summarises the findings from this work and discusses the strengths and limitations. Then addresses implications for future research using electronic health records for the study of diabetes drug prescribing.

2 Chapter 2: A systematic review comparing the evidence for kidney function outcomes between oral antidiabetic drugs for type 2 diabetes (Paper 1)

Chapter summary

- Kidney outcomes are an important consideration for clinicians treating people with type 2 diabetes as approximately 40% of people with diabetes develop kidney disease.(1)
- Widely cited clinical trials did not address the comparative effect of diabetes drugs for kidney outcomes.
- The aim of this chapter is to review and collate data from published studies that compares type 2 diabetes drugs, over the long term, for kidney-related outcomes.
- The paper identified just 15 eligible studies that made comparisons between oral antidiabetic drugs for renal outcomes. With most of the comparisons made between metformin and thiazolidinediones or metformin and sulfonylureas.
- The work confirmed that little evidence existed for comparative effects of oral type 2 diabetes drugs on renal outcomes.

2.1 Introduction to Paper 1

Much of the published RCTs for type 2 diabetes drugs are placebo-controlled short-term studies that demonstrate efficacy for reducing HbA1c. However, the ultimate goal of treatment is to reduce the long-term complications of diabetes. Clinicians must make many decisions when treating individuals, such as the best HbA1c target or optimal drug, and they must balance the risks and benefits of each choice.

The aim of this chapter is to focus on the medium to long-term effects of therapy and on comparisons of drugs against other available treatments. The paper extends a systematic review published in 2016 that covered a range of diabetes-associated outcomes including effectiveness, cardiovascular disease, and mortality.(62) The 2016 review noted that evidence for microvascular outcomes was limited.(62) The previous review did not address kidney events specifically, which are an important consideration for clinicians treating individuals with type 2 diabetes since around 40% will develop kidney disease.(1) Recent RCTs including EMPA-REG, CANVAS, CANTATA-SU and CREDENCE have shown that SGLT2is slow renal function decline.(55, 57, 86) Though EMPA-REG, CANVAS and CANTATA-SU did not investigate kidney disease as a primary endpoint. Since publishing this review, the CREDENCE trial showed that the canagliflozin group had a 34% reduction in risk for a composite renal outcome in people with type 2 diabetes and chronic kidney disease.(57) CREDENCE, EMPA-REG and CANVAS were all placebo-controlled studies and so did not compare the potential benefits of the SGLT2is against SUs or DPP4is.

We published the paper in Wellcome Open Research. It provides a systematic review of the comparative research that examined outcomes related to renal function, among people taking different type 2 diabetes drugs. Drug classes of interest were oral agents including metformin, sulfonylureas, DPP4is, SGLT2is and thiazolidinediones, as these are recommended by NICE at the first stages of treatment. To reflect the decisions faced by clinicians in choosing drugs, we excluded placebo-controlled studies and only included head-to-head comparisons.

After an extensive search, I selected fifteen studies (seven RCTs and eight observational studies). Large amounts of heterogeneity were apparent in the reporting of kidney function. Many studies have made comparisons between drugs used at different stages of drug intensification, predominantly between metformin, a first-line agent, and second-line drugs (SU, DPP4i or SGLT2is). There is a paucity of evidence in the literature examining comparative kidney outcomes for the newest drug classes, SGLT2is and DPP4is, that GPs commonly prescribe in the UK.

The supplementary files, including the PRISMA reporting checklist, search terms, additional information from studies, and study quality criteria referenced in the article and the approved Prospero protocol are in **Appendix 2**.

With a lack of data available for the comparative effects of kidney outcomes, widening the scope of the review would have been beneficial. In addition to kidney outcomes, other microvascular events are important to people with diabetes including neuropathy, retinopathy and amputations. As the recent clinical trial work has shown reduced renal outcomes, understanding the potential for the benefits on other microvascular outcomes would also be important.(55, 57, 86)

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Samantha Wilkinson
Principal Supervisor	Laurie Tomlinson
Thesis Title	Prescribing trends, utilisation and comparative effectiveness of antidiabetic drug therapies prescribed in UK primary care

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Wellcome Open Research		
When was the work published?	19 June 2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author on this paper. I participated by writing the protocol for the study, completing the search, reviewing the articles, extracting data and drafting the manuscript.

	My co-authors supported the work by advising on research design, reviewing articles, extracting data and commenting on drafts of the paper.

Student Signature: [redacted] **Date:** 05/09/2019

Supervisor Signature: [redacted] **Date:** 05/09/2019

SYSTEMATIC REVIEW

A systematic review comparing the evidence for kidney function outcomes between oral antidiabetic drugs for type 2 diabetes [version 1; peer review: 2 approved]

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Abstract

Background: The development of kidney disease is a serious complication among people with type 2 diabetes mellitus, associated with substantially increased morbidity and mortality. We aimed to summarise the current evidence for the relationship between treatments for type 2 diabetes and long-term kidney outcomes, by conducting a systematic search and review of relevant studies.

Methods: We searched Medline, Embase and Web of Science, between 1st January 1980 and 15th May 2018 for published clinical trials and observational studies comparing two or more classes of oral therapy for type 2 diabetes. We included people receiving oral antidiabetic drugs. Studies were eligible that; (i) compared two or more classes of oral therapy for type 2 diabetes; (ii) reported kidney outcomes as primary or secondary outcomes; (iii) included more than 100 participants; and (iv) followed up participants for 48 weeks or more. Kidney-related outcome measures included were Incidence of chronic kidney disease, reduced eGFR, increased creatinine, 'micro' and 'macro' albuminuria.

Results: We identified 15 eligible studies, seven of which were randomised controlled trials and eight were observational studies. Reporting of specific renal outcomes varied widely. Due to variability of comparisons and outcomes meta-analysis was not possible. The majority of comparisons between treatment with metformin or sulfonylurea indicated that metformin was associated with better renal outcomes. Little evidence was available for recently introduced treatments or commonly prescribed combination therapies.

Conclusions: Comparative evidence for the effect of treatments for type 2 diabetes on renal outcomes, either as monotherapy or in combination is sparse.

Keywords

Review, Kidney Diseases, Comparative Effectiveness Research, Diabetes Mellitus, Type 2, Hypoglycemic Agents

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 1 published 19 Jun 2018	✓ report	✓ report

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Any reports and responses or comments on the article can be found at the end of the article.

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First published: 19 Jun 2018, **3**:74 (https://doi.org/10.12688/wellcomeopenres.14660.1)

Introduction

Type 2 diabetes mellitus (DM) increases an individual's risk for health problems including cardiovascular disease, blindness, chronic kidney disease (CKD), and nerve damage[1–4]. The development of kidney disease is associated with other complications of type 2 diabetes and with poorer outcomes[1,3,5]. Therefore, slowing the development of, or preventing kidney disease is one aim of therapy[2]. Type 2 diabetes drugs are thought to play a major role in protecting the kidneys by controlling blood sugar levels and may confer additional protective effects according to specific drug profiles[3]. However, as kidney function declines, type 2 diabetes drug options become limited due to prescribing restrictions[2,3,5–7]. This presents a challenge for treating type 2 diabetes in patients with non-diabetic related kidney disease, as well as those with renal diabetic complications.

Treatment choice reflects a complex balancing of expected risks and benefits. A recent systematic review focused on vascular outcomes, glyclated hemoglobin (HbA1c), body weight, hypoglycaemia and common adverse events[8]. Here we focus on kidney-related outcomes as another important aspect of clinical care that clinicians must consider when prescribing drugs for type 2 DM. Our aim was to provide a summary of the current evidence of long term kidney outcomes, from comparative, long terms studies of oral antidiabetic drugs. We included the following outcomes: change in kidney function (estimated glomerular filtration rate), progression or development of proteinuria, development of end-stage renal disease (ESRD) and composite outcomes compared between different oral drugs for the treatment of type 2 DM.

Methods

The protocol for this systematic review was submitted, reviewed and approved by PROSPERO (International prospective register of systematic reviews, ref. 2016: CRD42016036646). The study was conducted and is reported in accordance with the PRISMA protocol (Supplementary File 1)[9].

Data sources and searches

We searched the databases; Medline, Embase and Web of Science for articles published between 1st January 1980 and 15th May 2018. The search comprised keywords and MESH terms relating to three broad themes: kidney function, type 2 diabetes drugs and clinical studies. We limited the search to English-language studies, and studies in humans. The search strategies are in Supplementary Table 1 and Supplementary Table 2 (Supplementary File 2). The reference lists of relevant reviews identified through the search were also screened.

Study selection

One reviewer (SW) screened all citations identified in the searches. Titles and abstracts for all studies were compared to the selection criteria. Then the full-text of selected studies were reviewed against the inclusion and exclusion criteria. Reviewer two (MI) was blinded to the articles selected by reviewer one and screened a 20% sample of the articles selected by reviewer one after the title screen. The studies chosen by the two reviewers were compared.

We defined the search and screening strategies before completing the searches. Studies were eligible for inclusion if they were clinical studies that (i) compared two or more classes of oral therapy for type 2 DM; (ii) reported kidney outcomes as primary or secondary outcomes; (iii) included more than 100 participants, and (iv) followed participants for 48 weeks or more. We restricted the review to oral antidiabetic drugs recommended at the initiation and first intensification of treatment[6].

We did not include studies that reported only placebo-controlled comparisons as we were interested in the difference in effects between active therapy regimes to reflect therapy choices made in routine clinical care; placebo-controlled studies would not estimate this difference. Our definition of a kidney outcome was broad to identify as many studies as possible. We accepted any kidney-related outcome, including the incidence of chronic kidney disease, reduced estimated Glomerular Filtration Rate (eGFR), increased creatinine, 'micro' and 'macro' albuminuria, proteinuria, end stage renal disease (ESRD) and composite kidney outcomes. We did not include composite microvascular outcomes that combined kidney outcomes with other microvascular outcomes such as retinopathy or neuropathy.

Data extraction and quality assessment

After study selection, using a predefined data collection tool, we extracted data for the following items: number of participants, study design, calendar years covered by the study, length of follow-up, drug comparison, mean age of study population, exclusion criteria for study, kidney measurements taken at baseline, mean duration of diabetes, mean HbA1c at baseline, primary outcome for the study, kidney outcomes reported and results for kidney outcomes reported. Reviewer one (SW) assessed each study for quality, using the GRACE 2014[10] items for observational comparative effectiveness research and the Cochrane Collaboration tool for assessing risk of bias in randomised trials[11] for RCTs.

Results

Figure 1 details the study selection process through which we found 9,086 potentially eligible studies. The first reviewer (SW) completed the initial title screen and selected 1,896 articles. The second reviewer (MI) was blinded and reviewed a 20% random sample of these articles. The agreement between reviewers was good, reviewer two selected an additional paper that was rejected after discussion. After subsequent discussions (SW, MI and LT), we selected 15 studies.

We identified 15 eligible studies, seven of which were randomised controlled trials (RCTs)[12–18] and eight were observational studies[19–26]. Across the 15 studies, three RCTs[16–18] and one observational study[22], reported changes in eGFR as an outcome. All seven RCTs[12–18] and two observational studies[22,25] investigated albumin-creatinine ratio (ACR) as an outcome. Six observational studies reported kidney endpoints, including kidney failure, nephropathy, acute dialysis and composite endpoints with eGFR[19–21,23,24,26]. Comparisons made, and outcomes studied are summarised graphically in Figure 2. Given the range of the kidney function outcomes reported and the drug class comparisons

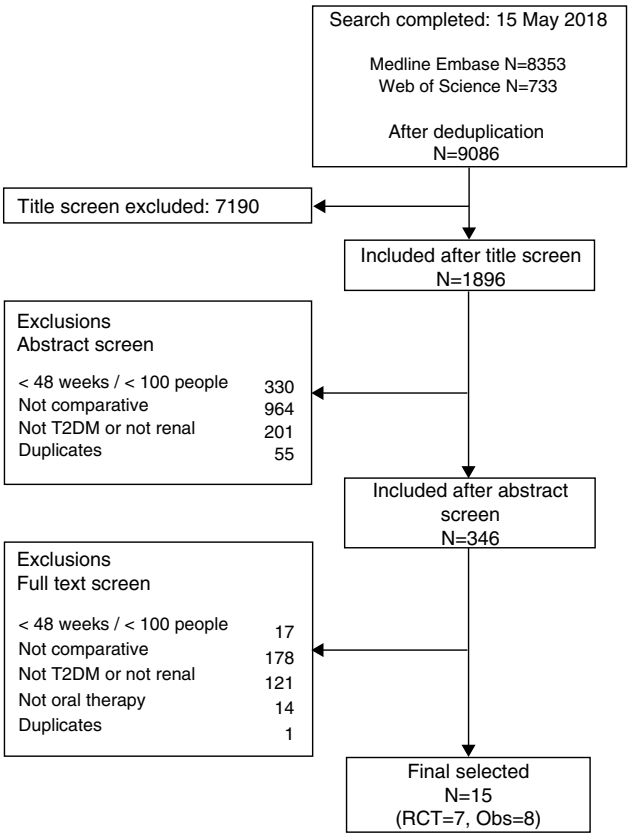

Figure 1. Flow diagram of study selection. Ovid was used to search the Embase and Medline databases.

made we did not complete a meta-analysis of the results, instead we provide a narrative summary of studies. Selected studies and their findings are summarised in Table 1 and Table 2.

In total, we identified 32 direct comparisons between oral drugs for the treatment of type 2 DM: 22 comparisons between monotherapies, three comparisons between dual therapy combinations, and seven comparisons between dual therapies and monotherapies, outlined in Table 3. One study compared many combination therapy options to metformin; we did not include the triple therapy combinations from this study in our results, details of the comparisons are in Supplementary Table 3 (Supplementary File 2)[23].

Monotherapy comparisons

Metformin monotherapy vs. thiazolidinedione monotherapy. The most common drug comparison was metformin monotherapy vs. thiazolidinedione monotherapy (five studies made seven comparisons)[14,16,19,22,23]. Two RCTs found that thiazolidinediones were associated with improved kidney outcomes (reduced proteinuria or improved eGFR) compared to metformin[14,16] while two observational studies found no differences between the two drug classes[19,22]. One observational cohort study showed that thiazolidinediones were associated with a higher risk for development of kidney failure (a composite of kidney dialysis, kidney transplant and CKD stage five) compared to metformin[23].

Metformin monotherapy vs. sulfonylurea monotherapy. Six observational studies[19–23,26] compared metformin monotherapy to sulfonylurea monotherapy. Though two of these studies (19 and 20) reported similar findings from the same source population, we have therefore only reported one of the results, making six comparisons. Four comparisons favoured metformin. One study found the risk of eGFR falling to below 60 mL/min/1.73m^2 was greater in the sulfonylurea group compared to the metformin group[22]. Three found higher risks of kidney failure outcomes (various composites of codes for nephropathy, dialysis, renal transplant, ESRD, and reductions in eGFR) for sulfonylurea compared to metformin[20,21,23]. One study, using proteinuria as an outcome, found no difference between drug classes[22]. One further study reported higher rates of acute dialysis for people initiating metformin compared to sulfonylureas[26].

Sulfonylurea monotherapy vs. thiazolidinedione monotherapy. Findings from two RCTs showed differences in ACR that were not statistically significant[12,16]. However, one of these studies also showed an increase in mean eGFR among patients treated with a TZD, but a fall in the SU group[16].

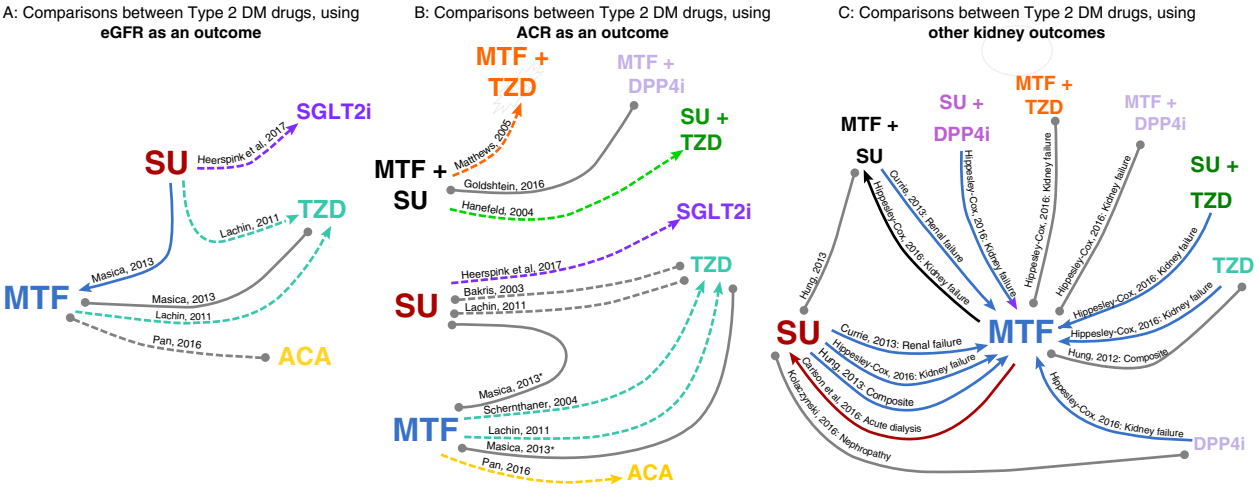

Figure 2. Graphical representation of drug comparisons and findings. Connecting lines indicate where studies have made comparisons between drugs. Lines connect drug names and are labelled with the authors that made the comparison. Dashed line indicates randomised studies, single line indicates non-interventional studies. Findings are indicated by the colour of the line: where one drug appears to be protective, the line is the colour of the protective drug. Grey lines indicate no significant difference. E.g. Blue lines connecting metformin to sulfonylurea indicate that metformin appeared to be protective of kidney function. Arrow heads point towards the drug that appeared to be protective. One further comparison not included here. Hung *et al.* 2012, as two studies by Hung *et al.* reported similar comparison using similar data* Also includes dipstick and urine protein tests, † metformin group largely metformin, but some taking TZD or SU. Abbreviations: MTF: metformin, SU: sulfonylurea, TZD: Thiazolidinedione, DPP4i: Dipeptidyl peptidase-4 inhibitor, ACA: acarbose, SGLT: Sodium-glucose Cotransporter 2 inhibitors, GLP1: Glucagon-like peptide-1 receptor agonist, eGFR: estimated Glomerular Filtration Rate, ACR: Albumin creatinine ratio, ARF: Acute renal failure.

Sulfonylurea monotherapy vs. SGLT2i monotherapy. One RCT showed canagliflozin slowed kidney function decline, and reduced albuminuria, compared to glimepiride[17].

Combination therapy comparisons

Only three studies compared combination therapies.

Metformin plus sulfonylurea vs. metformin plus thiazolidinedione. One RCT compared metformin plus sulfonylurea to metformin plus a thiazolidinedione[15]. They reported that ACR decreased in the metformin plus thiazolidinedione group and increased in the metformin plus sulfonylurea group[15].

Sulfonylurea plus metformin vs. sulfonylurea plus thiazolidinedione. One RCT compared sulfonylurea plus metformin to sulfonylurea plus thiazolidinedione[13]. The study found that the ACR increased in the sulfonylurea plus metformin group, and decreased in the sulfonylurea plus thiazolidinedione group[13].

Metformin plus sulfonylurea vs. metformin plus gliptin (DPP4i). One observational study compared metformin plus sulfonylurea combination therapy to metformin plus sitagliptin[25]. The results showed weak evidence that metformin plus sitagliptin improved the likelihood of reductions in ACR, with an odds ratio of 1.20 (95% CI: 0.99–1.47, P = 0.063)[25].

Dual therapy vs. monotherapy

Three observational studies made seven comparisons between monotherapy options and combination therapy[20,21,23]. One study indicated that people taking metformin were at a lower risk of renal failure compared to people taking metformin plus sulfonylurea[21]. Another study found the opposite, people taking metformin plus sulfonylurea were at lower risk of kidney failure compared to metformin[23]. The same study found no differences in the risk of kidney failure compared to metformin in people prescribed; i) metformin plus thiazolidinedione, and ii) metformin plus gliptin. They also reported that people prescribed sulfonylurea plus thiazolidinedione, and a sulfonylurea plus DPP4i were at higher risk for kidney failure compared to metformin[23].

Another observational study found no difference in eGFR outcomes between sulfonylurea monotherapy and metformin plus sulfonylurea combination therapy[20].

Study quality

We assessed each study for quality, using the GRACE 2014[10] items for observational comparative effectiveness research and the Cochrane Collaboration risk of bias tool for RCTs[11] Supplementary Table 5 and Supplementary Table 6 (Supplementary File 2) detail the results. For the RCTs, we assessed study quality as good, though few studies reported details of randomisation techniques. Of the observational studies, reporting was reasonable, according to the GRACE criteria. However, many of the studies made comparisons between drugs used at different stages of drug intensification, or between monotherapy and combination therapy. For example, two observational studies[21,23] used metformin monotherapy as the baseline in comparisons with combination therapy. As metformin monotherapy is the

Table 1. Summary of study characteristics: Randomised Studies.

Author (Year)	Number	Follow-up	Drug comparison*	Mean age (yrs)	Exclusions†	Inclusions†	Measures at baseline			Primary outcomes of study	Kidney outcomes recorded
							Kidney measures Proteinuria/ Mean ACR/ eGFR	Yrs with T2DM Mean (SD)	Mean HbA1c(%, SD)		
Bakris *et al* (2003)[12]	121[a]	52w	SU, TZD (GLY, RSG)	55.6	Prior use of ACEI, ARBs, BB or CCBs	40–80 yrs with type 2 DM	28% micro-albuminuria [b] Baseline ACR NR	NR	GLY: 9.5 (1.6) RSG: 9.1 (1.7)	Change in left ventricular mass index	52 w Microalbuminuria[b] resolved in: RSG: 43%, GLY: 6% ACR mean % change: RSG: -23, GLY: -8
Hanefeld *et al* (2004)[13]	639	52w	SU+TZD, SU+MTF (SU+PGZ, SU+MTF)	60	Previous cardiac events, malignant disease in 6 months before study. Previous treatment with MTF or TZD	35–75yrs with type 2 diabetes inadequately managed with SU monotherapy with HbA1c 7.5-11.0%	28% albuminuria[c] Mean ACR (SD) SU+PGZ: 0.07 (0.25) SU+MTF: 0.11(0.56)	7	SU+PGZ: 8.8 (0.98) SU+MTF: 8.8 (0.97)	HbA1c at week 52, FPG, Insulin and lipid profiles.	52 w Microalbuminuria[c] resolved in: SU+ PGZ: 10.2%, SU+MTF: 7.7% ACR mean % change: SU+ PGZ: -15, SU+MTF: +2
Schernthaner *et al* (2004)[14]	1199	12m	MTF, TZD (MTF, PGZ)	56.5	Use of thiazides but other antihypertensives allowed	People inadequately treated with di*et al*one, or HbA1c 7.5–11%	NR	3.3	PGZ: 8.7 (1) MTF: 8.7 (1)	HbA1c	52 w ACR mean % change: PGZ: -19, MTF -1
Matthews *et al* (2005)[15]	630	52w	MTF+TZD, MTF+SU (MTF+PGZ, MTF+GLZ)	56.5	Ketoacidosis, MI, TIA, stroke in the previous 6m; symptomatic heart failure; acute malabsorption or chronic pancreatitis; familial polyposis coli; malignant disease in past 10ys; substance abuse	Previously not managed with MTF monotherapy, HbA1c 7.5–11%. No previous treatment with insulin, gliclazide, pioglitazone, SU/ TZD	Mean ACR (SD) MTF+PGZ: 0.06 (0.14) MTF+GLZ: 0.05(0.16)	5.7	SU+Pio: 8.7 (0.1) SU+MTF: 8.53 (0.9)	HbA1c	52 w ACR mean % change: MTF+ PGZ: -10, MTF+GLZ: +6
ADOPT Lachin *et al* (2011)[16]	4351	5yrs	TZD, MTF, SU (RSG, MTF, GLY)	56.9	Significant liver disease, kidney impairment (serum creatinine males: >1.3mg, females: >1.2mg), history of lactic acidosis, angina, congestive heart failure uncontrolled hypertension	≥3yrs history of type 2 DM, FPG 7-10mmol/L.	16% albuminuria[c] Mean ACR (log transformed) RSG 9.9 (180), MTF 9.3 (172), GLY 9.4 (172) Mean eGFR (geometric): RSG 98.0 (24.6), MTF 97.1 (25.6), GLY 95.7 (27.6)		RSG: 7.36 (0.93) MTF: 7.36 (0.93) GLY: 7.35 (0.92)	Time to drug failure, using FPG	4 yr Albuminuriad resolved in: RSG: 69.5%, MTF: 64%, GLY: 64% ACR mean change (95% CI): RSG 2.1 (-4.2, 8.8), MTF 20.9 (13.3, 28.9), GLY 6.1 (-1.2, 14.0) eGFR mean change % (95% CI): RSG: 5.1 (3.6-6.7), MTF: 1.4 (0.0, 2.9), GLY: -0.4 (-2, 1.2)

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Author (Year)	Number	Follow-up	Drug comparison*	Mean age (yrs)	Exclusions†	Inclusions†	Measures at baseline			Primary outcomes of study	Kidney outcomes recorded
							Kidney measures Proteinuria/ Mean ACR/ eGFR	Yrs with T2DM Mean (SD)	Mean HbA1c(%, SD)		
Pan *et al* (2016)[18]	762	48w	ACA, MTF	50	History of cardiac disease, kidney disease, uncontrolled hypertension, urinary infection	Newly diagnosed type 2 diabetes within 1 yr: >1 month of treatment with type 2 diabetes in previous 12m and no treatment 3 months prior.	Elevated ACRe ACA 20%, MTF 24% Median ACR (IQR) ACA: 12.5 (4.9-25.8), MTF 11.6 (5.3-28.8) Mean eGFR (SD) ACA: 109.6 (29.8), MTF 114.9 (32.3)	ACA: 1.6, MTF: 1.7	ACA: 7.49 (1.25) MTF: 7.6 (1.23)	ACR, eGFR	Elevated ACRe Median ACR (IQR) ACA: 5.80 (0.9-13.2), MTF 7.31 (2.2-18.7) Mean eGFR (SD): ACA: 112.8 (32.6), MTF 114.6 (32.8)
CANTATA-SU Heerspink *et al* (2017)[17]	1450	104w	SGLT, SU (CNG, GLM)	56.2	eGFR >60, last 6 months severe hypoglycaemia, serum creatinine (µmol/L) (men >124, women >115), TZD in last 16 weeks	18-80 yrs with type 2 DM, HbA1c 7-9.5 %. managed with MTF therapy	Mean ACR (25th, 75), CNG 100mg: -2.7 (-3.5, -1.9), CNG 300mg: percentile) GLM: 8.2 (5.75, 17.98), CNG 100mg: 8.7 (5.74, 17.52), CNG 300mg: 8.6 (5.28, 20.64) Mean eGFR (SD) GLM: 89.5 (17.5), CNG 100mg: 89.7 (19.3), CNG 300mg: 91.4 (19.4)	6.6	GLM:7.8(0.8) CNG 100mg: 7.8 (0.8) CNG 300mg: 7.8 (0.8)	Change in albuminuria and kidney function	104w ACR mean % change, relative to GLM (SD): CNG 100mg: -5.7 (2.2, -13.1), CNG 300mg: -11.2 (-3.6, -18.3) eGFR Mean change (95 CI): GLM: -5.4 (-6.2, -4.5), CNG 100mg: -2.7 (-3.5, -1.9), CNG 300mg: -3.9 (-4.7, -3.0) Incidence of 30% eGFR decline HR (95% CI) Referent GLM CNG 100mg: 0.66 (0.42, 1.04), CNG 300mg:0.93 (0.62, 1.42)

Abbreviations: ACA: acarbose, ACEI: ACE Inhibitor, ACR: Albumin:Creatinine Ratio, ARB: Angiotensin receptor blocker, BB: beta-blocker, CCB: calcium channel blocker, CI: confidence interval, CNG: Canagliflozin, CV: coefficient of variation [100x(exp[SD-mean])], eGFR: estimated glomerular filtration rate, FPG: Fasting plasma glucose, GLY: glyburide, GLZ: Gliclazide, GLM: Glimepiride, IQR: Inter Quartile Range, MI myocardial infarction, MTF: metformin, NR: not reported , PGZ: Pioglitazone, RSG: Rosiglitazone, SU: sulfonylurea, SGLT: SGLT2i, SD: Standard deviation, TZD: thiazolidinedione, TIA: transient ischaemic attack

Notes: *Oral type 2 diabetes drugs only, †Summary inclusion and exclusion criteria only, a: N with ACR at baseline and by 52w, b: Defined as ACR 30 µg/mg or below [or 30mg/g], c: Not defined, d: ACR greater than or equal to 30mg/g, e: elevated ACR included 'micro' albuminuria (30-300mg/g) and 'macro' albuminuria (≥300mg/g)

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Table 2. Summary of study characteristics: Observational Studies.

Author (Year)	Number	Data source (Country)	Yrs of study	Drug comparison	Age (yrs)	Kidney related exclusions	Measures at baseline			Primary outcomes of study	Follow-up (yrs)	Kidney outcomes recorded HR (95% CI)[c]
							Kidney	Years with T2DM	HbA1c %			
Hung *et al.* (2012)[19]	93577	Veterans Administration (US)	2001–2008	Incident MTF, SU or RSG, excluding combination users	Median (IQR) MTF: 60 (55, 69) SU: 62 (56, 72) RSG: 64 (57, 72)	eGFR <60	Microalbuminuria[b] %: MTF: 3, SU: 3, RSG: 4 [only available for 15,065 people] Median eGFR (IQR) MTF: 81 (72, 93), SU: 80 (70, 93), RSG: 79 (69, 91)	NR	Median (IQR): MTF: 7.1 (6.5, 7.9) SU: 7.3 (6.6, 8.4) RSG: 6.8 (6.2, 7.6)	**1** eGFR (≥25% decline) **2** ESRD (eGFR<15, ICD-9 codes for dialysis or renal transplant) **3** Mortality	Median (IQR): MTF: 0.9 (0.5, 1.8) SU: 0.8 (0.4, 1.7) RSG: 0.7 (0.3, 1.5)	**eGFR event or ESRD** Referent MTF SU: 1.20, (1.13, 1.28), RSG: 0.92, (0.71, 1.18) **eGFR event, ESRD or mortality** Referent MTF: SU 1.20, (1.13, 1.28), RSG: 0.89, (0.69, 1.12)
Currie *et al.* (2013)[21]	84,622	CPRD GOLD datalink (UK)	2000–2010	MTF, SU, MTF+SU	Mean (median) 61.9 (12.8)	None stated	Creatinine >130 µmol/L: 4.5%	Mean: 2.3 (SD 3.0)	Mean (SD): 8.7 (1.9)	Renal failure (Read codes)	Mean: 2.8	**Renal failure** Referent: MTF SU: 2.63 (2.20, 3.15), MTF+SU: 1.39 (1.12, 1.72)
Hung *et al.* (2013)[20]	13238	Veterans Administration (US)	1999–2008	MTF, SU, MTF+ SU	Median (IQR) MTF: 59 (54, 67) SU: 60 (54, 71) MTF+SU: 58 (53, 65)	Serum creatinine >1.5 mg/dL or eGFR < 60	eGFR Median (IQR) MTF: 81 (72, 93) SU: 80 (71, 93) MTF+SU: 82 (73, 97)	NR	Median (IQR) MTF: 7.1 (6.5, 7.9) SU: 7.3 (6.6, 8.4) MTF+SU: 7.9 (6.8, 10)	**1** eGFR (≥25% decline) **2** ESRD (eGFR<15, ICD-9 codes for dialysis or renal transplant) **3** Mortality	Mean: 1.2	**eGFR event or ESRD** Referent: SU MTF: 0.85 (0.72, 1.01), SU+MTF: 1.01 (0.75, 1.37) **eGFR event, ESRD or mortality** Referent: SU MTF: 0.82 (0.70, 0.97), SU+MTF 1.05 (0.79, 1.40)

Author (Year)	Number	Data source (Country)	Yrs of study	Drug comparison	Age (yrs)	Kidney related exclusions	Measures at baseline			Primary outcomes of study	Follow-up (yrs)	Kidney outcomes recorded HR (95% CI)[a]
							Kidney	Years with T2DM	HbA1c %			
Masica *et al.* (2013)[22]	Proteinuria analysis: N=798 eGFR analysis: N=977 [IPW cohort]	Clinical data from primary care networks (US)	1998–2009	Exposure to drug (≥90d) MTF, SU, TZD, or combo	Mean (SD) MTF: 53.9 (11.9) SU: 53.7 (13.0) TZD: 53.9 (12.0) [Age at diagnosis, IPW cohort]	Baseline proteinuria or MDRD eGFR<60	eGFR Mean (SD) **Proteinuria analysis**: MTF: 82.3 (20) SU: 79.5 (23) TZD: 75.6 (16) **eGFR analysis**: MTF: 86.8 (18) SU: 86.2 (21) TZD: 91.4 (34)	NR	8.0 % IPW group	**1** New proteinuria (24-hour albumin/ protein, spot protein, spot ACR, or dipstick) **2** New eGFR <60	Proteinuria analysis: Mean: 3.2 eGFR analysis: Mean: 2.8	9% (72/798) developed proteinuria **Incidence of proteinuria** MTF referent SU: 1.27 (0.93, 1.74), TZD: 1.00 (0.70, 1.42) **Fall in eGFR to <60 (2)** MTF referent SU: 1.41 (1.05, 1.91), TZD: 1.04 (0.71, 1.50)
Hippisley-Cox and Coupland (2016)[23]	274,324 [N for kidney analysis not reported]	QResearch (UK)	2007 – 2015	DPP4i, TZD, MTF, SU, 'other agents'	Mean (SD) TZD: 63 (12) DPP4i: 63 (12) MTF: 64 (13) SU: 66 (13) Other: 60 (12)	Kidney disease at baseline, and severe kidney disease	NR for kidney analysis: prior to kidney baseline exclusions: Creatinine μmol/L mean (SD) TZD: 87 (34), DPP4I: 85 (33), MTF: 85 (30), SU: 92 (48)	% 1–3yrs since diagnosis: TZD: 28 DPP4I: 26 MTF: 25 SU: 24	Mmol/mol Mean (SD) TZD: 67 (19) DPP4i: 68 (18) MTF: 61 (19) SU: 65 (20) Other: 71 (20)	Incident severe kidney failure (Read codes for dialysis & transplantation, or CKD stage 5 based on serum creatinine values)	NR	**Incident severe kidney failure** MTF referent TZD: 2.55 (1.13, 5.74), DPP4i: 3.52 (2.04, 6.07), SU: 2.63 (2.25, 3.06), MTF+SU: 0.76 (0.62, 0.92), MTF+TZD: 0.71 (0.33, 1.50), MTF+DPP4i: 0.59 (0.28, 1.25), SU+TZD: 2.14 (1.27, 3.61), SU+DPP4I: 3.21 (2.08, 4.93)

Author (Year)	Number	Data source (Country)	Yrs of study	Drug comparison	Age (yrs)	Kidney related exclusions	Measures at baseline			Primary outcomes of study	Follow-up (yrs)	Kidney outcomes recorded HR (95% CI)[a]
							Kidney	Years with T2DM	HbA1c %			
Kolaczynski *et al.* (2016)[24]	5436 matched sample	IMS Lifelink (Germany)	2007–2013	SU, DPP4i	Mean (SD) SU: 63.7(10.7) DPP4i: 64.6 (10.9)	History of nephropathy	Renal failure % (ICD-10 code) DPP4i: 13 SU: 11.1	Mean (SD) DPP4i: 3.1 (3.4) SU: 3.2 (3.4)	Mean (SD) DPP4i: 7.61 (1.47), SU: 7.64 (1.37)	Incident nephropathy (ICD-10 code)	Mean (SD) DPP4i: 3.48 (3.75) SU: 2.49 (3.46)	**Incidence of nephropathy** Referent SU DPP4i 0.90 (0.72, 1.14)
Goldshtein *et al.* (2016)[25]	564 matched sample	Maccabi Health Service diabetes registry (Israel)	2008–2014	MTF+SU, MTF+DPP4i	Mean (SD) SU: 58.5 (11) DPP4i: 59.1 (11.2)	Dialysis, eGFR <45 or ACE/ARB in 90 day post index	ACR mg/g mean (SD) SU: 122.4 (194.5) DPP4i: 139.9 (261.9) eGFR mean (SD) SU: 84 (19.5), DPP4i: 82.4 (19.1)	Mean (SD) SU: 5 (3.5), DPP4i: 5.2 (3.5)	Mean (SD) SU: 8.6 (1.5), DPP4i: 8.5 (1.5)	Improvements in urinary ACR (≥20% improvement in ACR and change in KDIGO category)	Mean: 9 months, max 52 weeks	**ACR reductions** Referent MTF+SU MTF+DPP4i: 1.20 (0.99,1.47)
Carlson *et al.* (2016)[26]	168,443	All Danish citizens	2000–2012	MTF, SU	Mean (SD) MTF: 65.7 (9.4) SU: 69.2 (10.8)	ESRD or eGFR <30 ml/min/ 1.73m^2	eGFR Median (IQR) MTF: 74 (63–87) SU: 69 (57–82)	NR	NR	**1** Acute dialysis	1y following treatment initiation	**Acute dialysis** Referent: SU MTF: 1.51 (1.06–2.17)

Abbreviations: ACR: Albumin: Creatinine Ratio, eGFR: estimated glomerular filtration rate, ESRD: End Stage Renal Disease, ICD: International Classification of Diseases, MTF: metformin, SU: sulfonylurea, TZD: Thiazolidinedione, DPP4i: Dipeptidyl peptidase-4 inhibitor, RSG: Rosiglitazone, STG: Sitagliptin, EXE: Exenatide. IPW: Inverse Probability Weight, FU: Follow-up, SD: Standard deviation, ARF: Acute Renal Failure, CKD: Chronic Kidney Disease, IQR: Inter Quartile Range, p-yr: person-years, NR: Not reported, DB: Database, KDIGO: Kidney Disease: Improving Global Outcomes **Notes**: a: MACE: Major adverse cardiac event: non-fatal MI, non-fatal stroke, or cardiovascular death, b: microalbuminuria if ACR was >30 mg/g, c: Hazard Ratio (HR), Mantel Haenszel (MH) or Odds Ratio (OR), eGFR units: mL/min/1.73m^2

Table 3. Results summary.

			RCTs		Observational	
			Number	Results	Number	Results
ACR						
Monotherapy						
MTF	vs	**ACA**	**1**	**Favours ACA**	0	
MTF	vs	**SU**	0		1	No difference
MTF	vs	**TZD**	**2**	**Both favour TZD**	1	No difference
SU	vs	**SGLT**	**1**	**Favours SGLT**	0	
SU	vs	**TZD**	2	Both no difference	0	
Dual therapy						
MTF+SU	vs	**MTF+DPP4i**	0		1	No difference
MTF+TZD	vs	**MTF+SU**	**1**	**Favours MTF+TZD**	0	
SU+TZD	vs	**SU+MTF**	**1**	**Favours SU+TZD**	0	
eGFR						
Monotherapy						
MTF	vs	**ACA**	1	No difference	0	
MTF	vs	**SU**	0		**1**	**Favours MTF**
MTF	vs	**TZD**	**1**	**Favours TZD**	1	No difference
SU	vs	**SGLT**	**1**	**Favours SGLT**	0	
SU	vs	**TZD**	**1**	**Favours TZD**	0	
KIDNEY OUTCOMES						
Monotherapy						
MTF	vs	**DPP4i**	0		1	**Favours MTF**
MTF	vs	**SU**	0		**4**	**3 favour MTF, 1 favours SU**
MTF	vs	**TZD**	0		2	1 no difference, **1 favours MTF**
SU	vs	**DPP4i**	0		1	No difference
Mono vs. dual therapy						
MTF	vs	**MTF+DPP4i**	0		1	No difference
MTF	vs	**MTF+SU**	0		2	**1 favours MTF, 1 favours MTF+SU**
MTF	vs	**MTF+TZD**	0		1	No difference
MTF	vs	**SU+DPP4i**	0		**1**	**Favours MTF**
MTF	vs	**SU+TZD**	0		**1**	**Favours MTF**
SU	vs	**MTF+SU**	0		1	No difference

Abbreviations: ACR: Albumin: Creatinine Ratio, eGFR: estimated glomerular filtration rate, MTF: metformin, SU: sulfonylurea, TZD: Thiazolidinedione, DPP4i: Dipeptidyl peptidase-4 inhibitor, ACA: acarbose, , EXE: Exenatide. SGLT: SGLT2i, GLP1: Glucagon-like peptide-1 receptor anonist, IPW: Inverse Probability Weight, FU: Follow-up, SD: Standard deviation, ARF: Acute Renal Failure, CKD: Chronic Kidney Disease, IQR: Inter Quartile Range, p-yr: person-years, NR: Not reported, DB: Database, KDIGO: Kidney Disease: Improving Global Outcomes. One further comparison not included here. Hung *et al.* 2012, as two studies by Hung *et al.* reported similar comparison using similar data

most common drug for initiating treatment, and the addition of other drugs to metformin is likely to be associated with progression or poor control of type 2 DM, comparing metformin to drug prescribed at the first stage of intensification is problematic, particularly for renal outcomes. Those people receiving treatment intensification will tend to be sicker, and distinguishing between the effects of treatment and the effects of the underlying disease may not always be possible.

Conclusion

Key findings

Overall, we have found a lack of consistent evidence of long-term differences in kidney outcomes between T2DM drugs. In comparisons of treatments for type 2 DM, for thiazolidinediones vs metformin, there is some evidence of reduced proteinuria - of four comparisons with ACR as an outcome (in combination or monotherapy), three favoured TZD and one showed no difference. Most evidence from observational research also suggested that metformin is associated with better kidney outcomes than sulfonylureas.

Despite frequent use of combination therapies for the treatment of diabetes, we found few studies that compared commonly used dual therapies that investigated renal outcomes.

Previous work

The finding that thiazolidinediones may reduce proteinuria compared with metformin is aligned with observations of other authors and supported by animal studies[27,28]. Though previous evidence is limited, other work suggests that TZDs could exert reno-protective effects via a number of pathways, including reducing blood pressure[28]. TZDs may also act directly in the kidneys via proliferator-activated receptor gamma (PPARg), found in the kidney (and in other tissue)[27,28]. However, changes in estimated GFR may reflect changes in fluid status rather than true changes in renal function, which was not measured directly in any study[29].

Strengths

To our knowledge, this is the first systematic review of the comparative research literature that investigated the effects of type 2 diabetes drug regimens on renal function. We have conducted an extensive and detailed search, with broad definitions of renal function.

Limitations

We have focused on renal outcomes only but recognize this is just one of many safety and effectiveness factors to be considered when deciding treatment options. Despite the importance of careful monitoring and maintenance of kidney function for people with diabetes, we identified just 15 long-term studies reporting renal outcomes. Renal complications of type 2 diabetes take many years to develop after the onset of diabetes and studies may not be adequately powered or have sufficient length of follow-up to detect differences. Therefore, many studies have used the surrogate marker of changes in proteinuria as a marker of clinical renal outcomes. Further, initial changes in kidney function may be misleading. One included study indicates benefits of canagliflozin over glimipiride for kidney function decline at 104 weeks: however these benefits were not apparent until 52 weeks[17,30]. This and the EMPA-REG study[31] have indicated initial acute falls in eGFR with better outcomes compared to placebo only observed over the longer term so this would not be apparent in short-term studies.

Our review included both randomised and non-interventional studies. Whilst the unique inferential advantages of randomization are clear, our review highlights a large overall difference in population size depending on study type: randomised trials generally included hundreds of patients, whilst non-interventional studies often had tens of thousands of participants. Rarer outcomes such as ESRD are therefore more likely to be detected in non-interventional settings. This highlights their important role, but the evidence generated from them needs to be evaluated cautiously due to the potential for bias and confounding.

The available evidence does not reflect drugs currently prescribed in routine care. In our review, 69% (22/32) of the comparisons, contrasted different monotherapies, with just three comparisons between dual therapy combinations. In clinical practice, metformin is the most common first-line therapy, and GPs now rarely prescribe thiazolidinediones (EU marketing authorization for Rosiglitazone was suspended in 2010[32], following concern regarding increased heart failure risk)[33].

In the UK, NICE guidance recommends the addition of sulfonylureas, Dipeptidyl peptidase-4 inhibitors (DPP4is) Sodium-glucose Cotransporter 2 Inhibitors (SGLT2is), or TZDs to metformin, yet, just one study compared these combinations (MTF+SU vs MTF+DPP4i)[25,33–35]. Recent studies that have shown potentially exciting improvements in renal outcomes for patients treated with SGLT2is were conducted against placebo and so were not eligible for this study[36,37].

We found that definitions of kidney outcomes were not consistent across studies. Definitions of renal decline in the observational studies relied upon either codes for kidney disease (e.g. diabetic nephropathy, acute renal failure), surrogate markers (e.g. eGFR or proteinuria) or a combination of codes and tests, summarised in Supplementary Table 4 (Supplementary File 2). For the albuminuria data, which has a skewed distribution, most studies used logarithmic transformation to approximate normal, yet not all studies applied this method[18]. Such differences between outcomes will limit future opportunities for pooling effect estimates in meta-analyses. Different approaches to study design may also limit the validity of findings. We found two observational studies that made the same comparisons yet found different effects. Both examined renal failure, using UK primary care data, (QResearch[23] and Clinical Practice Research Datalink[21]). They found comparable effect sizes when comparing the use of sulfonylurea monotherapy to metformin monotherapy, for renal failure (2.63, 95% CI: 2.25, 3.06[23] and 2.63, 95% CI: 2.19, 3.15[21]). However, when comparing sulfonylurea plus metformin dual therapy to metformin monotherapy, estimates of the risk of kidney failure were in opposite directions (0.76, 95% CI: 0.62, 0.92[23] and 1.39, 95% CI: 1.12, 1.72[21]). Difficulties in adjusting for levels of diabetic control or change in renal function that led to these treatment choices (confounding by indication), may explain these conflicting results.

In the randomised controlled studies, we found that eligibility criteria were strict. Many studies excluded people most at risk of kidney outcomes e.g. those with reduced kidney function or cardiovascular disease[12,13,15–18]. These restrictions limit the generalisability of study findings to routine clinical settings where

people presenting with diabetes have complex comorbidities[38]. Further, as most individuals with type 2 diabetes will receive treatment for other comorbid conditions, prescribers need to know how diabetic therapies interact with concomitant drugs, yet this is not addressed by the studies identified in this review.

Clinical relevance

In clinical practice, kidney function is one of many considerations for treatment choice in type 2 DM. Some of the differences we found for albuminuria and eGFR between people taking different oral therapies for type 2 diabetes were statistically significant, but the clinical importance of these findings may be limited. Some surrogate outcomes such as a doubling of creatinine or 30% decline in eGFR are closely associated with risk of future ESRD[39,40] while ACR is not[39,41,42]. Outcomes that are clinically relevant need to be assessed in future studies. Ideally, these should include hard outcomes such as hospital admission with acute kidney injury or the development of ESRD. Therefore, large, well-designed studies with long follow up, including individuals that represent the typical type 2 diabetes population, will be required. However, the incidence of kidney outcomes is likely to be low in most randomised trials and therefore high-quality observational studies will also be needed.

Our review highlights a lack of rigorous studies comparing the effects of oral type 2 diabetes drugs on kidney outcomes, in particular, for the newer drug intensification options where prescribing is rapidly increasing.

Data availability

All data underlying the results are available as part of the article and supplementary material no additional source data are required.

Competing interests

SW is funded by a GSK PhD scholarship. HS is an employee of and holds shares in GSK. LAT reports no competeing interests. IJD is funded by, holds stock in and has consulted for GSK. LS is funded by a fellowship from the Wellcome Trust and consults for GSK and AstraZeneca, has received grants from the European Union and is a Trustee of the British Heart Foundation.

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Supplementary material

Supplementary File 1 – Completed PRISMA checklist

Click here to access the data.

Supplementary File 2 – File contain the following supplementary tables.

Click here to access the data.

Supplementary Table 1: First Ovid Medline search

Supplementary Table 2: First search Web of science

Supplementary Table 3: Report of further comparisons from Hippisley-Cox and Coupland (2016) paper

Supplementary Table 4: Detailed definitions of composite renal outcomes for observational studies

Supplementary Table 5: GRACE 2014 items for observational studies

Supplementary Table 6: Cochrane items for quality of RCT studies

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3 Chapter 3: Methods

Chapter summary

- This chapter describes the data sources used for each study detailed in **Chapters 4-6**: the UK Clinical Practice Research Datalink GOLD dataset, and mortality and Index of Multiple Deprivation (IMD) data from the Office of National Statistics.
- It covers how data is generated in clinical practice and then processed into a research database.
- This is followed by the methods applied to identify eligible people, covariates, outcomes, and the steps taken to reduce bias in the studies.

3.1 Source of Data

3.1.1 Overview of the UK Clinical Practice Research Datalink

The primary source of data for this thesis is the UK Clinical Practice Research Datalink (CPRD GOLD). CPRD GOLD is a database of electronic medical records collected in routine clinical practice from select GP practices in the UK (England, Scotland, Wales and Northern Ireland). As of July 2017, there were 17,148,866 patients, sourced from 718 practices in the UK that have contributed data since 1987, of these, the CPRD central processing team deemed 14,942,430 to be 'up-to-standard'. Approximately 2.3 million patients are registered at practices contributing data.(87) CPRD GOLD covers around 7% of the UK population and is used extensively for a range of pharmacoepidemiological studies.(88)

In the UK, NHS primary care provides the 'gateway' into NHS specialist care for most patients, apart from those attending emergency services, some sexual health clinics and some private care. About 99% of the population are registered with a GP practice.(92) Care through the NHS is free at the point-of-care, paid for via tax contributions. Outpatients pay a flat fee for prescriptions in England (£9 as of April 2019), which is waived for people with exempt status.(89) Around 90% of prescriptions provided by the NHS are free of charge. People can gain exemption from charges if they are over 60 or under 16, pregnant or recently pregnant, or have long-term medical conditions which includes people with diabetes.(90) In Scotland, Wales and Northern Ireland, all prescriptions are free.

Primary care data recording

Healthcare providers in GP practices use computer software to record details of consultations, medical history and treatment. GPs act as the entry point into the NHS, they generally know of major health events in a person's life as hospital staff update GPs with diagnoses and treatments provided. GPs hold records for their patients covering many years, which is valuable to researchers investigating long-term exposures and clinical outcomes.

Use of electronic health records in UK primary care became widespread in the late 1980s. The department of health encouraged practices to adopt electronic record keeping with subsidisation and by requiring electronic records for payments-by-performance incentives. There are several systems available to practices, including Egton Medical Information Systems (EMIS), Vision and SystmOne.(91) Several systems are translated into anonymous, research ready databases. CPRD GOLD uses records from Vision practices, and others collect data from practices using Vision (The Health Improvement Network [THIN] database), EMIS (CPRD Aurum), or SystmOne (ResearchOne). However, practices must actively provide data to each database, and so coverage of each database relies upon participation. Further, practices can change their computer system provider, meaning that patients can appear in multiple databases.(91)

Though not collected for research, data quality is important for clinicians. These records are the primary means to record patient interactions within the practice and for maintaining a history of an individual's health status. In addition, the Department of Health uses the information to audit clinical standards and to administer the Quality Outcomes Framework (QOF). The Department of Health introduced QOF in 2004 to incentivise GPs to provide health interventions that improve health

outcomes. These incentives apply to a range of important health domains, including diabetes, and help to standardise both care provision and health status recording across a number of diseases.(92, 93)

Data quality

The CPRD ensures that data submitted by practices meet quality standards.(88) In the CPRD GOLD database, individuals with records of adequate quality are labelled 'acceptable'. Records must include sufficient follow-up, a registration status (not temporarily registered), age and gender information. Practices must also meet 'up to standard' requirements ensuring that data collection is consistent and that mortality rates are similar over time.(88, 94)

Data structure

The CPRD database holds data in a series of data files: Therapy, Clinical, Patient, Immunisation, Referral, Test, Additional and Consultation files. Each file provides data for different aspects of patient care, detailed in **Table 3.1**. Each CPRD table are linkable using either patient identification numbers, consultation identification number, or a code that links additional information to test or clinical records.

Data table	Data contained within the file	Records per patient
Patient	Includes gender, year of birth, marital status, ethnicity information, dates included in CPRD data, and death dates.	Contains one record for each subject identified in the data extract.
Therapy	Records of prescriptions given to patients by primary care prescribers. Includes product name, prescription duration, date of prescription and dosage information.	Can have multiple or no records for each patient in extract.
Clinical	Diagnoses, signs and symptoms coded with Read codes	Multiple or no records for each patient.
Immunisation	Records of immunisations.	Multiple or no records for each patient.
Referral	Referrals to a hospital or other care settings, and urgency.	Multiple or no records for each patient.
Test	Details of tests or measures taken in primary care, and results.	Multiple or no records for each patient.
Consultation	Details of the clinical staff member that the patient consulted with.	Multiple or no records for each patient.
Additional	Details that can be linked to test or clinical files. Includes a wide variety of items such as test results (e.g. serum creatinine) and lifestyle choices (e.g. smoking status) and symptoms.	Multiple or no records for each patient.

Table 3.1 Description of the CPRD GOLD data structure, and data available within each table

To extract study populations from CPRD GOLD, researchers use diagnostic, medical, procedure or drug prescribing codes, to find eligible individuals. They code medical diagnoses, symptoms, procedures and history using the Read code system, developed by James Read in the early 1980s and first introduced to the NHS in 1985.(95, 96) Read codes provide a structured way for researchers to identify clinical characteristics. Vision software prompts GPs to provide a Read code before they can enter clinical information. Therefore, the Read code system should enable

researchers to identify most clinical events in an individual's history, apart from those in free-text as detailed in **Section 3.2**.

For exposure status, this project relies upon drug prescribing. Vision software codes drug prescriptions with product and British National Formulary (BNF) codes. To provide a drug to a patient, the GP must generate a prescription using the software, which automatically populates various prescription details. For this reason, prescriptions in the therapy file are essentially complete, apart from drugs that are given over-the-counter.(97) In studies that compared therapy records in CPRD to national prescription data or other sources of primary care data, prescribing rates were similar.(98-101)

The CPRD can also provide linkage of records to other sources of health data, whilst maintaining the anonymity of the patient record. NHS Digital act as the data custodian and processes linkages to maintain anonymity, methods for linking data sources are published.(94)

3.1.2 ONS

The completeness of mortality data in the CPRD can be limited, as reporting of deaths to GP practices is not legally required. It is an important concern for practices to record mortality, for example, to avoid causing distress to relatives by attempting to contact deceased people.(102) Completeness and accuracy of mortality information may differ according to how patients presented to the healthcare system. Data held by the UK Office of National Statistics (ONS) is the most accurate source of mortality information, as all deaths in England and Wales must be reported to the local authority within 5 days, and the law mandates this.(103) CPRD researchers therefore commonly request linkages to information from the UK ONS to access

more complete mortality information.(88) Gallagher et al. investigated the estimates of mortality after Venous Thromboembolism (VTE) in CPRD and linked datasets. Their work indicated that some deaths following VTE were missing from primary care records; estimates increased from 169.9/1000 person-years in HES-linked CPRD data to 173.2/1000 person-years when these individuals were linked to UK ONS mortality records.(103)

3.1.3 Index of Multiple Deprivation and Hospital Episode Statistic data

The ONS also provides estimates of socio-economic status, in the form of the index of multiple deprivation (IMD), for around 75% of practices that consent to linkage.(88) The IMD is a composite of multiple facets of an individual's life and opportunities: housing, income, employment status, education, health, disability, and crime.(104) This data is available for patient or practice postcodes and linked to Lower Layer Super Output Area (LSOA)-level deprivation measures.(104) For this thesis I used the latest LSOA-level deprivation measures available, created in 2015.

Other data linkages available from CPRD include the Hospital Episodes Statistics Database (HES). HES data is a source of administrative health data, for hospital admissions in England. CPRD can provide linkage to HES data, however, HES is only available for around 75% of CPRD practices and this would limit the study size and generalisability.(88) As GPs could only prescribe newer drug options recently, maintaining a maximum number of eligible patients was a priority. Therefore, HES linkage was not sought for this project.

3.2 Strengths and limitations of CPRD data

As previously stated, CPRD offers a population-based representative sample of electronic medical records for the UK population. However, some important information is missing from the records that is important to acknowledge.

GPs use Read codes to classify inputs into the electronic health record, as detailed above. However, once a GP starts a record, they can enter clinical information as free-text. This free-text entry is not available to researchers as this field may contain personal information that could identify patients. As researchers are unaware of information recorded in the free-text field, they may miss clinical information not recorded in a structured way. This could lead to an underestimation of outcome rates, or prevalence of baseline covariates.(105)

Some facets of a patient's health status are not available in CPRD GOLD. For example, frailty is a measure of vulnerability to health outcomes linked to age. Frailty that may be apparent to a GP, and thus inform their prescribing practice, has not to date been recorded in the electronic record.(106) Where frailty is linked to both prescribing and outcomes, this could introduce confounding.

Vision software automatically includes information about prescriptions, as outlined in **Section 3.1.1**. However, adherence of patients to GP instructions and whether the individual collects the prescription is not available.

People may exhibit a range of behaviours with drugs whilst collecting prescriptions, from strict adherence to only taking the medicines rarely. The veracity with which an individual follows a drug prescription extends to other drugs on their prescription. An individual that takes their diabetes drugs in a variable way will also likely take their antihypertensive medications inconsistently.(107) Misclassification of

exposures will bias estimates. If this is not differential between drugs, effect estimates will be biased towards the null. If some patient characteristics associated with adherence also affect the choice of prescription, bias could be introduced via more complex mechanisms in unpredictable directions.

People do not tolerate some drugs, leading them to stop taking it as prescribed and changing drugs. Using an intention-to-treat design would estimate effects of the drug in clinical practice but would not reflect the 'as-treated' experience. Therefore, when selecting people for each drug cohort I sought to minimise this source of exposure misclassification by selecting patients that received more than one prescription, and censored patients when they received prescriptions for other drugs indicating switching of treatment, **Section 1.1**.

Primary care data is a good source of information given that most people with type 2 diabetes receive most of their care in the community. However, some patient data may be incomplete or not recorded. This is a particular problem for variables such as body mass index (BMI), blood pressure, renal function, lifestyle factors, and ethnicity. Missingness of these items can often be associated with engagement in care and future outcomes.(108-110) For example, BMI information could be missing due to an individual not engaging with health seeking behaviours, or their GP. These people would have fewer BMI measures over time in their GP record, contribute less data to the analyses and have worse outcomes. If GPs are more willing to prescribe newer drugs to those more invested in health-seeking behaviours, then newer drugs will be associated with fewer outcomes and effect estimates biased.

In 2004, the QOF began incentivising GPs to meet a range of targets when treating diabetes, including annual checks for BMI and renal function. Since QOF, an

increasing proportion of people with diabetes had a serum creatinine recorded between 1997 and 2010.(93) For the years that BMI recording was incentivised by QOF 2004-2013, annual BMI recording rates were above 90%, up from approximately 80% in 1998.(111, 112) Incentivisation of BMI ceased in 2013, and recording of BMI fell to 83% in 2017.(108, 112)

3.3 Data management

I processed, managed and analysed data using Stata MP (Version 14.2). For some tables and graphics I used R (Version 3.5.0) and RStudio.

3.3.1 Data protection

Though CPRD data is pseudonymised, European and UK data protection laws demand that use of CPRD GOLD data is approved by an ethics and scientific committee before starting work. I stored all patient-level data on university approved, secured and regularly backed-up servers and only used the data for the purposes of the approved work.

3.4 Creation of diabetes drug code list

To identify treatment cohorts for this thesis, I used GP prescribing records for type 2 diabetes drugs. Therefore, an important first step in data processing was to create an up-to-date list of type 2 diabetes drugs. I achieved this with the following steps:

1. Identify initial list of products and British National Formulary (BNF) headers, or header codes from a literature search. The BNF is a source of prescribing, pharmacology and safety information for drugs approved for use in UK clinical practice.

2. Search CPRD CodeBrowser tool using the search terms related to type 2 diabetes drugs, detailed in **appendix 3.1**.

3. Manually assign drug class to each item in the list, full drug code list provided in **appendix 3.2**.

3.4.1 Creation of covariate definitions

Identifying individuals in CPRD, and extracting data on their clinical history requires code lists that reflect the information of interest. This section provides an overview of the steps taken to identify covariates for each analysis. First, I used published disease code lists from departmental colleagues, CALIBER or ClinicalCodes.org. CALIBER is a research collaboration with a focus on cardiovascular disease that share code lists and Stata do. files which they have used in research. Clinicalcodes.org is a resource that collates published clinical codes and accompanying papers. As new clinical codes and new drug products are introduced over time, I updated and checked code lists. To update code lists, I took the following steps: i) search the medical code dictionary provided by CPRD, using inclusion and exclusion terms based on literature searches, ii) compare the identified records to the source code list, iii) reviewed possible new codes with clinicians (Laurie Tomlinson and Liam Smeeth). **Figure 3.1** illustrates the generic process.

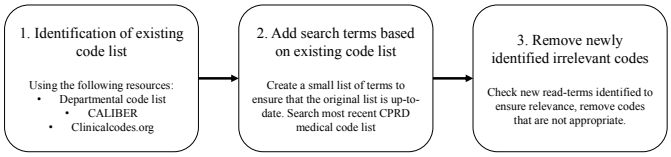

Figure 3.1 Step-wise generic process for creating diagnostic code lists using and updating existing code lists

Code lists for each manuscript are published online at the LSHTM Data Compass: http://datacompass.lshtm.ac.uk/.

3.5 Exposure classification

Each analysis presented in this thesis relies upon creating cohorts of individuals taking specific medications that are at the same stage of treatment, which requires interpretation of prescribing patterns from patient records. In addition to the commonly recognised sources of selection and information bias, 'time-related' biases are an important consideration for pharmacoepidemiological studies.(113, 114)

Two common sources of time-related bias in cohort studies include:

1. Misclassification of person-time as exposed but where the individual cannot have an outcome (e.g. death) due to the exposure status being defined by an event which occurred later (e.g. a repeat prescription).(113) Known as Immortal time bias

2. Comparing treatments used at different stages of disease, sometimes referred to as time-lag bias.

Authors have criticised recent observational studies of SGLT2is for making comparisons between drugs used at different stages of treatment intensification: For example, SGLT2is vs. insulins. People at earlier stages of treatment are expected to survive longer with fewer morbidities compared to those at later stages of treatment who have had the disease for longer.(77)

An important foundation for this thesis is identifying treatment cohorts that are similar in terms of disease status, treatment stage and prior treatment.

3.5.1 Identifying people at the first stage of treatment intensification

Central to this research project was an investigation of the drugs prescribed at the first stage of type 2 diabetes treatment intensification. The first stage treatment

intensification cohort was used across three studies (**Papers 2, 3 and 4**). Exposure classification in each manuscript relied upon prescribing patterns, with minor differences in inclusion criteria according to the aims of each study. The inclusion criteria shared by all papers are provided in **Table 3.2**, and described below.

Inclusion criteria	Exclusion criteria
• Labelled 'acceptable' by CPRD with age and gender • Aged 18 years and over • 12 months of follow-up in health record before initial type 2 diabetes prescription • Record of any type 2 diabetes therapy between January 2000 and July 2017 • The first type 2 diabetes prescription in therapy records must be metformin monotherapy. • Intensified treatment with oral antidiabetic drugs	• Initiated treatment for type 2 diabetes with combination therapy. i.e. if prescribed metformin on the same day as another antidiabetic drug • Evidence of pregnancy in the 12 months before or after drug intensification.

Table 3.2 Inclusion and exclusion criteria for all first-stage intensification cohorts included in this thesis

Labelled 'acceptable' by CPRD with age and gender: First, to ensure data quality would be of a sufficient standard we only extracted data for individuals labelled as 'up-to-standard' by the CPRD processing team.

Aged 18 years and over: Only adults were eligible for the study as NICE treatment guidance is different for children with type 2 diabetes. I wanted to ensure that all individuals included were subject to the same set of treatment recommendations.

12 months of follow-up in health record before initial type 2 diabetes prescription: This ensured that all individuals were new-users of type 2 diabetes drugs. Ensuring that all individuals had 12 months of no treatment before their first type 2 diabetes drug minimises the misclassification of prevalent users as incident users.(113, 115)

Record of any type 2 diabetes therapy between January 2000 and July 2017: Over these years, treatment guidelines have changed. The first paper in the series describes changes in prescribing practice over this period. In subsequent papers, I limited the period of interest by only include people intensifying treatment in more recent years to ensure that they were subject to the same treatment recommendations and so were comparable.

The first type 2 diabetes prescription in therapy records must be metformin monotherapy: This criterion was chosen for two reasons. i) NICE clinical guidance recommends the use of metformin monotherapy as first-line treatment, unless contraindicated. People starting treatment with drugs other than metformin, may not be eligible for metformin for medical reasons, such as low kidney function.(18) In 2013, 91% of people in the UK started treatment with metformin.(19) Though this limits generalisability, metformin was the most common first line treatment used in the UK. This also ensured that the vast majority of people in the study have type 2 diabetes, though misclassification of people with late onset type 1 diabetes may still have occurred.

Intensified treatment with oral antidiabetic drugs: To ensure that individuals are intensifying, rather than switching treatment we checked for further prescribing of metformin after the second line drug was prescribed. By requiring that GPs prescribed metformin following the first stage of intensification, I reduce the number of people that have switched from metformin therapy to another monotherapy option, and therefore not treated according to NICE guidance for treatment intensification.

In addition, as NICE only recommends treatment with oral antidiabetic drugs at the first stage of treatment intensification, I focussed on these individuals. Though **Paper 2** provides counts of all drugs, including insulin and GLP-1s that are delivered subcutaneously, following metformin monotherapy. This helps to ensure that people were comparable in their disease severity and thus reduces time-related bias. This criterion also reduces misclassification of people with type 1 diabetes as being type 2. Approximately 13% of people aged 30-50 years, with a new diagnosis have type 1 diabetes, and require insulin.(116) Research suggest that GPs sometimes incorrectly treat these individuals for type 2 diabetes.(117, 118) These people incorrectly treated with metformin can become unwell and are then changed to insulin monotherapy.(118) Therefore, even though these individuals may have been included in the initiation cohort I have excluded them in the first stage intensification cohort.

***Excluded if* initiated treatment for type 2 diabetes with combination therapy. I.e. If GPs prescribed metformin on the same day as another antidiabetic drug.**
As metformin monotherapy is the only recommended course of treatment at treatment initiation, people initiated with combination therapy were also excluded. These people were treated outside of the guidelines and may have had very high

blood glucose or other complicating factors. This would make them inappropriate comparisons for people starting treatment with metformin alone.

Excluded if **there was evidence of pregnancy in the 12 months before or after drug intensification:** Amongst people receiving type 2 diabetes treatments, some may be pregnant or breastfeeding.(119) In this situation NICE recommends the use of insulin or metformin only, and recommend that GPs stop other antidiabetic drugs.(120) To account for this, I excluded individuals with a pregnancy code at the time, or within 12 months, of intensification. Of those with a record of pregnancy close to the point of treatment intensification, 96% had received intensification with insulin, which was expected given NICE prescribing recommendations.

3.5.2 Interpretation of prescribing patterns

Across the three studies, the first stage intensification cohort requires a specific temporal prescribing pattern to ensure that individuals are treated on a common pathway and that they are at the same stage of treatment.

All individuals must have received a single metformin monotherapy prescription, followed by a prescription for another antidiabetic drug class, followed by, or coinciding with, a further metformin prescription, **Figure 3.2**.

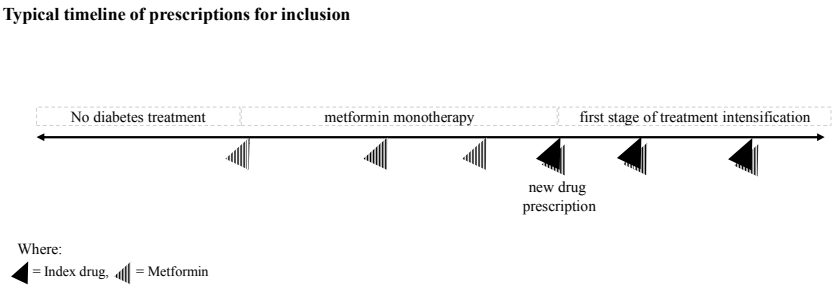

Figure 3.2 Typical pattern of prescriptions for inclusion in study. Each individual shows a period of no diabetes prescriptions, then metformin monotherapy indicating initiation of treatment, followed by prescriptions for further drugs alongside metformin.

There are three analyses presented in this thesis

1. A study of prescribing trends for oral antidiabetic therapies in the UK (**Paper 2, Chapter 4**)

2. A drug utilisation study showing patient level factors associated with prescribing (**Paper 3, Chapter 5**)

3. Comparative cohort study of the effects of the drugs on eGFR, BMI, systolic blood pressure (BP) and HbA1c (**Paper 4, Chapter 6**)

Each has differing aims, which led to minor differences when using therapy records to define inclusion. **Table 3.3** details the differences in the aims of each paper, and interpretations of treatment patterns, further illustrated in **Figure 3.3**.

Paper	Aim of study	Considerations for treatment definition	Treatment pattern
2: Study of trends in usage	Describe prescribing numbers at initiation of treatment and at treatment intensification over years	Distinguish treatment intensification from treatment switching to appropriately describe prescribing practices	Check the 60-day period, after the first stage of intensification, for further metformin prescriptions to ensure that they are intensifying rather than switching treatment
3: Drug utilisation	Understand what patient characteristics, apparent to the GP at the time of prescribing, influence treatment choice	Distinguish treatment intensification from treatment switching to ensure comparisons made between treatment groups are appropriate	
4: Cohort study	Understand how treatment is associated with subsequent outcomes	Distinguish treatment switching from intensification to ensure appropriate comparisons **AND** Ensure that included individuals have a sufficient window of exposure to intensification treatment	Check for further metformin within selected period **AND** Require a second prescription for the index drug within a reasonable* time period after initial drug prescription

Table 3.3 Similarities and differences in the assessment of treatment patterns for each study

*Defined in **Section 3.5.3.**

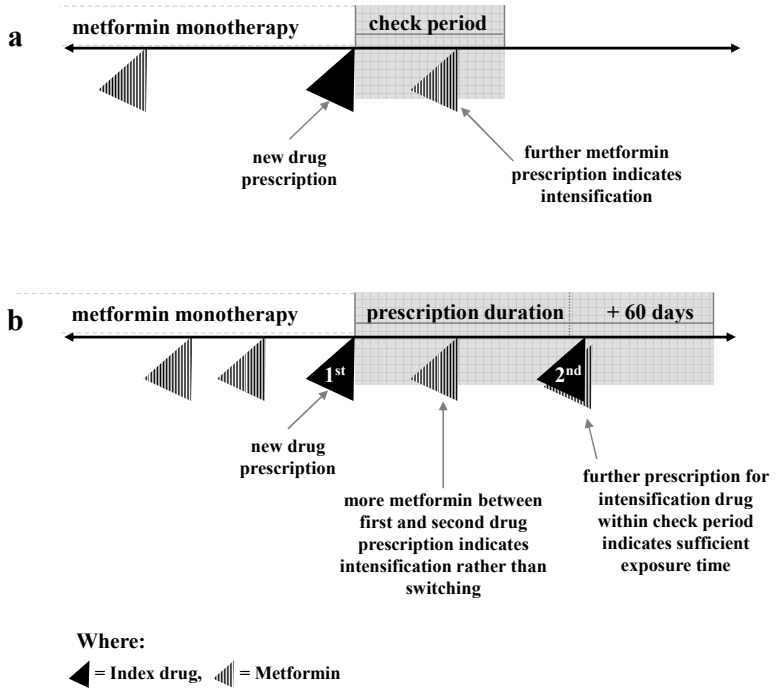

Figure 3.3 Illustration of differences in definition of treatment according to prescribing patterns in therapy records.

Timeline **a** shows simple inclusion criteria for Papers 2 and 3, and timeline **b** shows additional requirements implemented for Paper 4.

3.5.3 Interpretation of prescribing for cohort study (Paper 4)

Inclusion criteria are more complex for the cohort study presented in paper 4, to ensure that individuals have received more than a single prescription for the intensification drug. I developed a method where each person has a personalised check period where I expected to find further prescriptions.

If the duration of the initial prescription was short, I expected to find further drug prescriptions within a short period to interpret the prescriptions as a

course of treatment, and when the prescription duration was long, I allowed for longer check periods. The aim was to interpret prescribing patterns more accurately than using a generic 60-day check period for all patients. This was important as early analyses showed wide variation in the length of the initial drug prescription that was associated with the drug prescribed at intensification. I found that GPs prescribed initial insulin treatment for a mean of 6 days (SD: 5), compared to 40 days (SD: 17) for SUs. This GP decision may have been influenced by the complexity of drug delivery or likelihood of adverse reactions.

To implement this dynamic inclusion criterion, with a different check period for each individual, the steps were:

1. Identify the date of drug intensification (index prescription).
2. Calculate the duration of the prescription.
3. Determine the period from the first index prescription and the end of that prescription, add 60 days; this is the 'check period'.
4. Examine the 'check period' for further index drug prescriptions.
5. Identify the date of the further index drug prescription (if any, within the check period).
6. Check for metformin prescriptions between the first and second index drug.

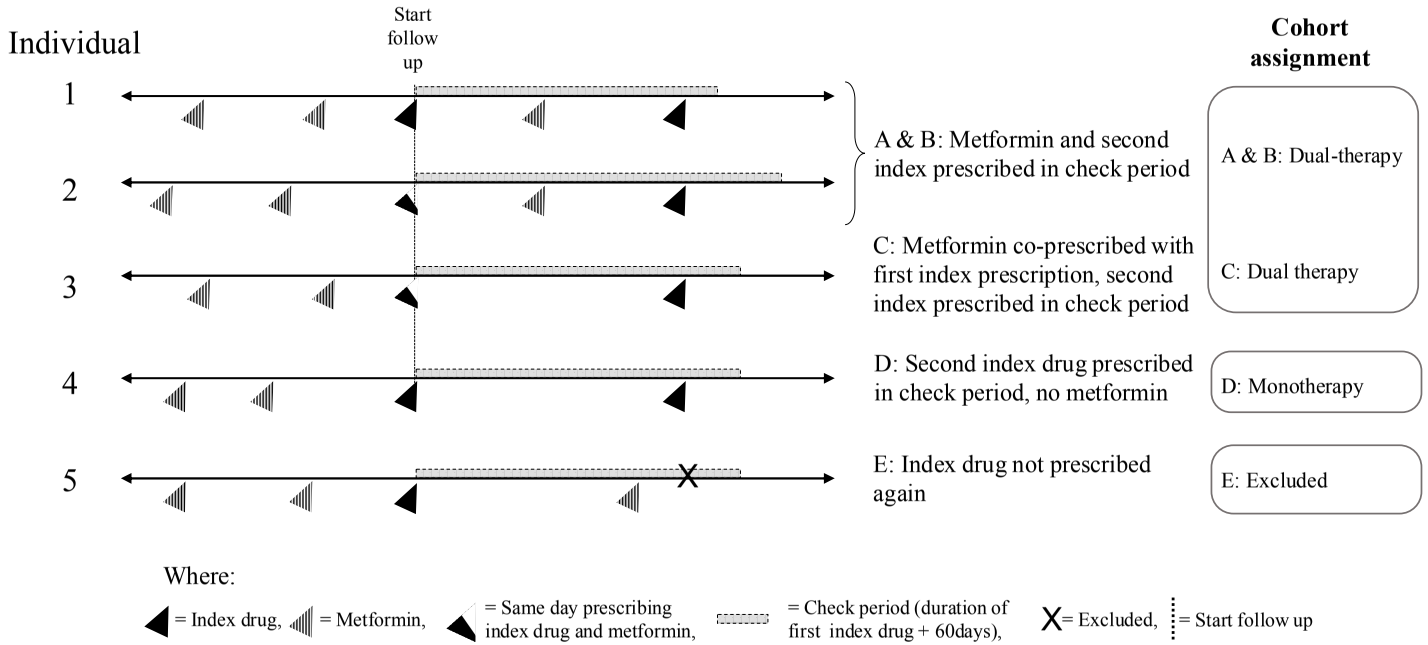

Figure 3.4 Treatment cohort assignment for paper 4. Five examples (1-5) of prescribing patterns observed in therapy records, and different cohort assignment (A-E) based on study inclusion criteria.

This method assigns people to three groups for each index drug:

(i) Dual therapy users,

(ii) Monotherapy users, and

(iii) An excluded group.

Follow-up starts when the individual received the first prescription for an intensification drug.

3.5.4 Sensitivity analyses of cohort definition

Using temporal prescribing patterns for cohort assignment has meant that 'information from the future' informs treatment assignment. For **Papers 3** and **4**, follow-up starts (or individuals are described) at the first prescription for an intensification drug. This means that I use future data to inform treatment cohort. An individual might die or leave the practice during the check period, resulting in that person being incorrectly excluded as someone that switched treatment when the GP intention was actually intensification. As people need to survive long enough to receive further prescriptions the effect would be that the most unwell people are dropped and do not contribute data. So individuals that do make it into the study are 'immortal' during the two prescriptions.

To investigate the potential impact of this we included a sensitivity analysis in **Paper 3 (Patient level factors associated with prescribing)**. I included all people that were censored or died in the 60 days after prescription of the first line treatment intensification drug. The results and further details of this are presented in **Section 5.2**.

For **Paper 4 (Comparative study of drugs on continuous variables)**, I started follow-up on the date of the first intensification prescription. This approach was favoured over the alternative of starting follow-up only when the GP prescribed a second intensification drug, as I would miss early changes in clinical measures in the analysis of outcomes. For example, if HbA1c quickly reduced in the month after treatment intensification, starting follow-up only at the point that a second drug was prescribed would miss clinically important changes in HbA1c.

3.5.5 Missing duration information

The check period required a valid duration for each prescription. CPRD prescribing records contain treatment duration (number of days or calculated from numeric daily dose and quantity). Of over 15 million type 2 diabetes prescriptions for individuals who met the initial inclusion criteria, duration information was missing in 27% (4,145,944/ 15,582,351) of all prescriptions.

To overcome this, I imputed missing durations using the most common prescription duration, using prescriptions that were similar based upon factors that might influence the length of a prescription. The factors expected to be associated with prescription length were chosen following discussions with a GP (Adrian Root, LSHTM):

Prescription year

Practice ID

Drug class

Whether it was the first prescription for the individual

We expected prescription year to influence duration, as GPs are likely to prescribe newer drug classes with more caution than those that they have many years of experience with. We also expected that drug class would be associated with prescription length, driven by typical pack sizes. The rationale for using the practice was that we expected GPs in a given practice to be influenced by the same prescribing rules, and therefore likely to use similar durations. If the drug was the first provided to a person, we predicted that GPs would initially prescribe for a short period in case of adverse reactions. We used the modal duration rather than the mean, as the mode would resemble the prescribing days generally used by prescribers, while the mean might be influenced by uncommon durations of treatment. Across all prescriptions, the most common duration used was 28 days (63%), followed by 56 days (25%) and 7 days (5%).

First, if a prescription was missing a duration, but given on the same day as another diabetes drug with one, I gave both the same duration. I then matched prescriptions on the factors above, and found the modal duration for those with non-missing durations. I filled the missing durations with the calculated mode. Where a matched group was not available, I matched the prescription on a smaller number of factors, until the duration could be filled with the mode. Therefore, if a matched group was not available based on prescription year, practice ID, drug class, and first prescription (Y/N), and then I sought matches using a smaller selection of variables. **Figure 3.5** illustrates the process.

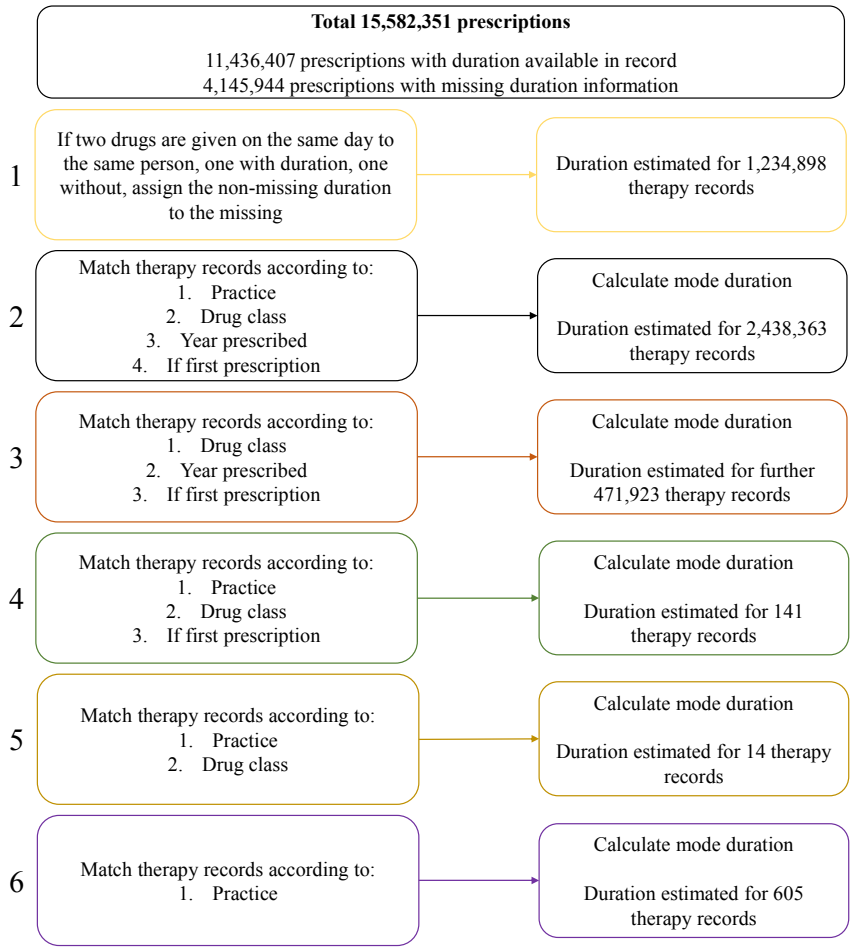

Figure 3.5 Steps taken to estimate missing duration information. Using all records available in the therapy file for individuals identified as being in receipt of type 2 diabetes drug prescriptions.

To assess the accuracy of the duration estimates, I compared the predicted durations to the known durations. Of 11,436,407 prescriptions with known durations, predicted durations underestimated duration by a mean of 0.42 days (SD: 14.61).

After we developed the method above, a study was published in 2016 that compared different methods for imputing missing duration: (i) replace all missing durations with 28 days, (ii) mode duration by drug strength and the number of tablets, and (iii) a machine-learning algorithm.(121) The paper compared these methods and concluded that both the mode duration and the machine-learning algorithm accurately estimated missing duration information. In addition, the subsequent effect estimates were comparable across all three approaches.(121)

4 Chapter 4: Changing use of antidiabetic drugs in the UK: Trends in prescribing 2000-2017 (Paper 2)

Chapter summary

- The treatment options for type 2 diabetes are changing. Between 2000 and 2017, regulatory bodies removed the thiazolidinedione rosiglitazone from the market, and drug companies developed new drug classes, the DPP4is and the SGLT2is.
- Given the changing nature of the prescribing options, the aim of this chapter is to describe the frequency of drug prescriptions in UK primary care, at treatment initiation and at the first stage of intensification, over time.
- The study shows increasing use of metformin at initiation, from 41% (95% CI: 40, 43) in 2000 to 89% (95% CI: 88, 90) in 2017.
- In 2017 the DPP4is were prescribed more than SUs for intensification of metformin monotherapy. DPP4is accounted for 42% (95% CI: 38, 47) of intensifications compared to the SUs at 30% (95% CI: 25, 35).
- Recommendations differ according to kidney function, and prescribing also changed over time. This chapter shows that in 2016 the most common drugs used to initiate treatment among people with an eGFR less than 30 ml/min/1.73m^2 were SUs (43%, 95% CI: 42, 44) and DPP4is (33%, 95% CI: 32, 34).

4.1 Introduction to Paper 2

This chapter provides a descriptive analysis of changing prescribing practices in the UK in primary care for type 2 diabetes treatment, both at drug initiation and at the first stage of drug intensification.

Understanding frequency of prescribing, adherence to recommendations, and potential channelling of drugs provides crucial information for interpretation of the subsequent outcomes study. Though prior research had described trends in prescribing, we found no published papers of prescribing trends for the most recent years, since SGLT2is entered the UK market at the end of 2012.(122)

The first set of UK guidelines became available in the UK in 2002, and favoured metformin as first line treatment. Between 2007 and 2017, two new drug classes have become available in UK primary care. Whilst one drug from the TZD class, rosiglitazone, was suspended from the EU market. In response to this and new evidence of benefits, treatment guidelines changed. In 2015, NICE published the most recent recommendations, which added SGLT2is to the range of drugs for treatment intensification.

The following paper is published in BMJ Open and describes prescribing patterns over time, both at treatment initiation, and for the first stage of treatment intensification. As part of this, I examined whether prescribing reflected changing guidelines. This included examining whether recommendations to avoid metformin for people with very poor renal function were followed. We also investigated the drug classes used at the first stage of treatment intensification and how prescribing patterns differ according to geographical area of the UK. Supplementary files associated with the paper are provided in **Appendix 3**.

Following **Paper 2**, in **Section 4.4** I present a description of prescribing over time according to the specific drugs prescribed within each drug class.

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RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student	Samantha Wilkinson
Principal Supervisor	Laurie Tomlinson
Thesis Title	Prescribing trends, utilisation and comparative effectiveness of antidiabetic drug therapies prescribed in UK primary care

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	BMJ Open		
When was the work published?	28th July 2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author on this paper. I participated by writing the protocol for the study, extracting and analysing data and drafting the manuscript. My co-authors supported the work by advising on research design, reviewing articles and commenting on drafts of the paper.

Student Signature: [redacted] **Date:** 02/09/2019

Supervisor Signature: [redacted] **Date:** 05/09/2019

BMJ Open

Changing use of antidiabetic drugs in the UK: trends in prescribing 2000–2017

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ABSTRACT

Objectives Guidelines for the use of drugs for type 2 diabetes mellitus (T2DM) have changed since 2000, and new classes of drug have been introduced. Our aim was to describe how drug choice at initiation and first stage of intensification have changed over this period, and to what extent prescribing was in accord with clinical guidelines, including adherence to recommendations regarding kidney function.

Design Repeated cross-sectional study.

Setting UK electronic primary care health records from the Clinical Practice Research Datalink.

Participants Adults initiating treatment with a drug for T2DM between January 2000 and July 2017.

Primary and secondary outcome measures The primary outcomes were the proportion of each class of T2DM drug prescribed for initiation and first-stage intensification in each year. We also examined drug prescribing by kidney function and country within the UK.

Results Of 280 241 people initiating treatment with T2DM drugs from 2000 to 2017, 73% (204 238/280 241) initiated metformin, 15% (42 288/280 241) a sulfonylurea, 5% (12 956/280 241) with metformin and sulfonylurea dual therapy and 7% (20 759/280 241) started other options. Clinicians have increasingly prescribed metformin at initiation: by 2017 this was 89% (2475/2778) of drug initiations. Among people with an estimated glomerular filtration rate of ≤30 mL/min/1.73 m^2, the most common drug at initiation was a sulfonylurea, 58% (659/1135). In 2000, sulfonylureas were the predominant drug at the first stage of drug intensification (87%, 534/615) but by 2017 this fell to 30% (355/1183) as the use of newer drug classes increased. In 2017, new prescriptions for dipeptidyl peptidase-4 inhibitors (DPP4i) and sodium/glucose cotransporter-2 inhibitors (SGLT2i) accounted for 42% (502/1183) and 22% (256/1183) of intensification drugs, respectively. Uptake of new classes differs by country with DPP4is and SGLT2is prescribed more in Northern Ireland and Wales than England or Scotland.

Conclusions Our findings show markedly changing prescribing patterns for T2DM between 2000 and 2017, largely consistent with clinical guidelines.

Strengths and limitations of this study

- ► This study uses contemporary UK primary care data to examine how prescribing at the first stage of treatment intensification for type 2 diabetes after metformin monotherapy has changed from 2000 to 2017.
- ► Using long-term prescribing data has enabled us to compare people at the same stage of treatment.
- ► We may have included some patients with type 1 diabetes, and may have wrongly classified some people who were changing rather than intensifying treatment.

INTRODUCTION

In the UK, the vast majority of prescribing for type 2 diabetes mellitus (T2DM) is undertaken within primary care. The aim of treatment is to reduce hyperglycaemia and morbidities associated with T2DM, such as cardiovascular disease and microvascular complications such as chronic kidney disease (CKD) or retinopathy.[1 2] National Institute for Health and Care Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) provide clinical guidance for the management of T2DM. After lifestyle changes, both NICE (NG28) and SIGN (154) recommend a series of intensification steps, adding drugs to a baseline of metformin monotherapy and only stopping metformin if there are clinical reasons to do so.[1 2] Estimates suggest that 30%–50% of people who started treatment on metformin monotherapy in the USA and Europe went on to further drug intensification.[3 4]

There are an increasing number of potential drug classes for the first stage of intensification after metformin monotherapy. Two new drug classes have recently been introduced: dipeptidyl peptidase-4 inhibitors (DPP4is; first licensed in the UK in 2007) and sodium-glucose cotransporter-2 inhibitors (SGLT2is first licensed in the UK in 2012). Guidelines have been updated to reflect these new options (figure 1).[1 2 5 6] Sulfonylureas (SU), SGLT2is, DPP4is and thiazolidinediones (TZD) are the current drug options for the first stage of drug intensification and are associated with different risk profiles and possibly specific benefits.[7 8] In light of the changing treatment guidelines, we aimed

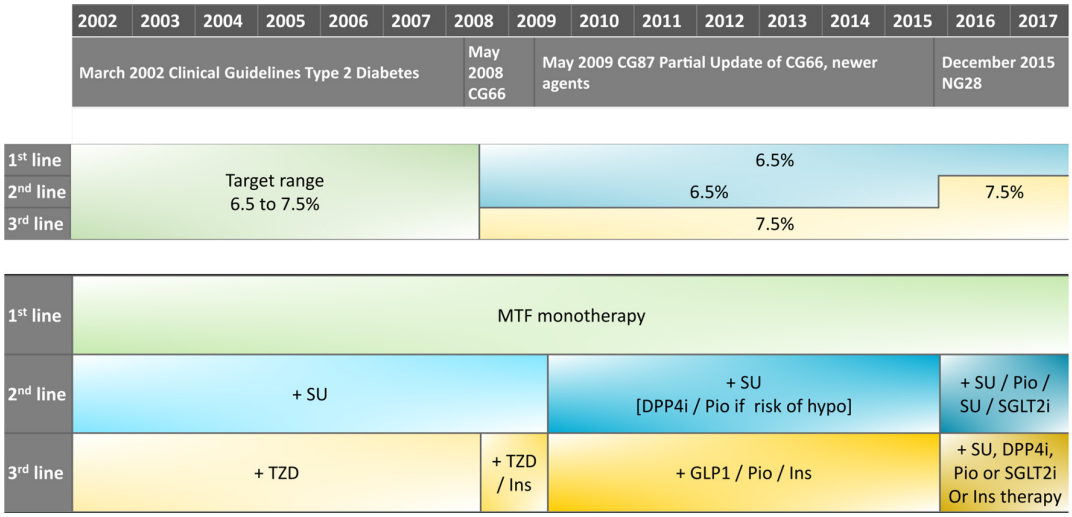

Figure 1 Changing National Institute for Health and Care Excellence (NICE) recommendations for type 2 diabetes mellitus (T2DM) drug treatment. CG, clinical guideline; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP1, glucagon-like peptide-1; Ins, insulin; MTF, metformin; NG, NICE guideline; Pio, pioglitazone; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.[1 2 5 6 14 21 33 34]

to describe patterns of prescribing using UK primary care data between 2000 and 2017, examining trends in prescribing at treatment initiation and at the point of first drug intensification, and to investigate the degree of concordance with guideline recommendations, in particular in relation to kidney function. In secondary analyses, we have explored whether there is variation in local practice by describing prescribing according to geographic location and clusters of general practices.

METHODS

Study setting

This observational study used data from the UK Clinical Practice Research Datalink (CPRD), a source of pseudonymised primary care health data which is regularly audited to ensure quality. CPRD data include demographic and lifestyle factors, records of prescriptions, clinical and test records and referrals to secondary care. The data come from primary care providers in England, Wales, Scotland and Northern Ireland and have been used extensively for clinical and pharmacoepidemiology studies, with previous validation studies suggesting that diagnoses coded in CPRD are highly reproducible from other data sources.[9 10]

Participants

We identified all individuals aged ≥18 years who started drug treatment for T2DM between 2000 and 2017. Although the onset of T2DM is typically over the age of 40 years, the age of diagnosis is decreasing over time, and earlier onset (and longer duration) is associated with poorer patient outcomes. We therefore only excluded the very young who are substantially more likely to have type 1 diabetes mellitus (T1DM).[11] We specified that patients should be registered at a general practitioner (GP) practice recording research quality data for a period of 12 months before starting drug treatment for diabetes to restrict the cohort to only new users of T2DM drugs.

We excluded women with a record of pregnancy (within 12 months either side of baseline prescription) as UK prescribing guidelines recommend different drug regimens for pregnant and breastfeeding women compared with other patients with T2DM.[12 13]

Codes to identify T2DM drugs were created based on British National Formulary T2DM chapters and drug codes are provided in the online supplementary file and on LSHTM compass, http://datacompass.lshtm.ac.uk/649/. We used the CPRD data released in July 2017.

Definition of exposure, outcome and covariates

Drug initiation cohort

We described prescribing for two cohorts of patients. The first included individuals who received any prescriptions for their first antidiabetic drug. We identified the first T2DM drug prescribed in their patient record. Where more than one drug was prescribed on the day of initiation, the treatment was recorded as a combination therapy of the drugs prescribed.

First stage of drug intensification cohort

Metformin is the only drug recommended by NICE and SIGN for drug initiation, with further drugs subsequently added if greater glycaemic control is required at the first stage of intensification. Therefore, we went on to describe prescribing among patients who intensify treatment after a period of metformin monotherapy. We described the first new drug prescribed after metformin monotherapy without any time limit. We sought to do this and exclude those who switched treatment by requiring that included individuals had a further prescription for metformin within 60 days of the prescription for a new drug class.

We did not describe further prescribing for patients who switch treatment from metformin as our focus is on treatment intensification rather than switching.

Covariates

For both cohorts we investigated how prescribing has changed over time by describing patterns for each calendar year, with year based on the day that the initiation or first intensification drug was first recorded in the patient record. Metformin is contraindicated for those with an increased risk of lactic acidosis such as those with reduced kidney function. Therefore, we also described treatment patterns for people with reduced renal function: (1) in individuals whose most recent estimated glomerular filtration rate (eGFR) was ≤30 mL/min/1.73 m^2 prior to drug prescription to reflect current treatment guidance, and (2) individuals with a serum creatinine higher than 130 µmol/L prior to drug prescription, to reflect guidance from 2002 that used this higher serum creatinine target.[14 15] eGFR was calculated using the last creatinine result, recorded not more than 540 days (18 months) prior to the date of treatment prescription, since we expected creatinine to be measured annually as recommended during the study period by Quality Outcomes Framework[16] and the National Diabetes Audit.[17] We calculated eGFR using the CKD-EPI equation[18] excluding the ethnicity factor as this is not entered in CPRD for a substantial proportion of individuals.[19]

To assess country-level differences, we stratified prescribing according to the location of each general practice: England, Northern Ireland, Scotland and Wales. We also described first stage of intensification prescribing according to Clinical Commissioning Group (CCG) groupings. CCGs are groups of GP practices that are responsible for commissioning local health services for patients, and may have shared management protocols or prescribing guidance. Here, GP practices are identified to be in the same CCG but there is no other identifiable information on the location of the CCG.

Statistical analysis

To examine how drug prescribing changed over time we first described patterns using counts of drug initiations between 2000 and 2017 with total prescribing for each year as the denominator. Then, we repeated this for the first stage of intensification prescribing patterns. We described initiation prescribing in the subgroup of individuals with reduced renal function, and we provided prescribing patterns for the first stage of intensification according to country and CCG. We calculated 95% CIs for the proportions using the standard normal distribution approximation. For people intensifying treatment in 2016, we calculated the mean time between starting metformin and the second treatment, we restricted to 2016 as this was the final year with complete data, and restricting to a single year reduced differential lead time due to non-availability of newer drugs in previous years.

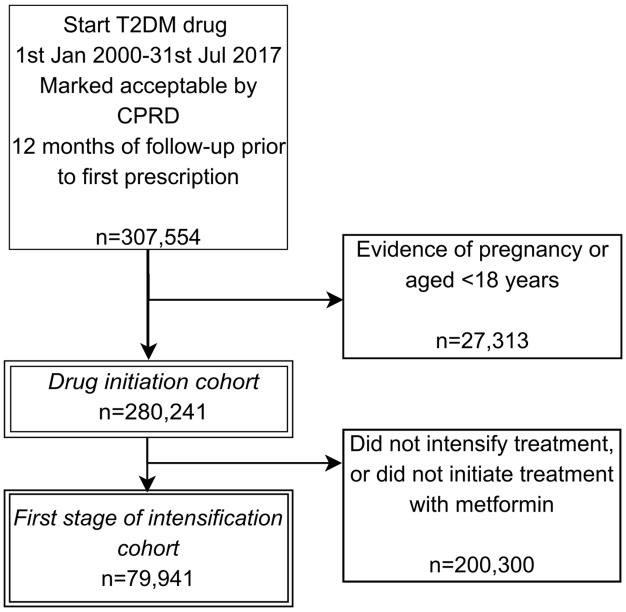

Figure 2 Flow diagram showing the creation of the cohorts and reasons for exclusion. CPRD, Clinical Practice Research Datalink; T2DM, type 2 diabetes mellitus.

Data extraction and processing of CPRD data was completed in Stata MP (V.14). All data analyses were completed using R and R packages for reproducible research. We reported our findings according to the RECORD reporting guidelines.[20]

Ethical and scientific approval

The research protocol was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol number 16_267). The protocol was made available to reviewers for peer review. Ethical approval for observational research using CPRD GOLD with approval from ISAC has been granted by a Health Research Authority Research Ethics Committee (East Midlands-Derby, REC reference number 05/MRE04/87). This study was also approved by the London School of Hygiene and Tropical Medicine Ethics Committee (reference 11923).

Patient and public involvement statement

Patients were not involved in the design or conduct of the study. We plan to disseminate the results through peer review publication.

RESULTS

We identified 280 241 people initiating treatment with an antidiabetic drug between the start of 2000 and July 2017. Inclusions and exclusions are shown in figure 2. Of those initiating treatment, 204 238/280 241 (73%) initiated with metformin monotherapy, 42 288/280 241 (15%) with SU monotherapy and 12 956/280 241 (5%) with metformin and SU dual therapy. Insulin monotherapy represents 6771/280 241 (2%) of initiations for

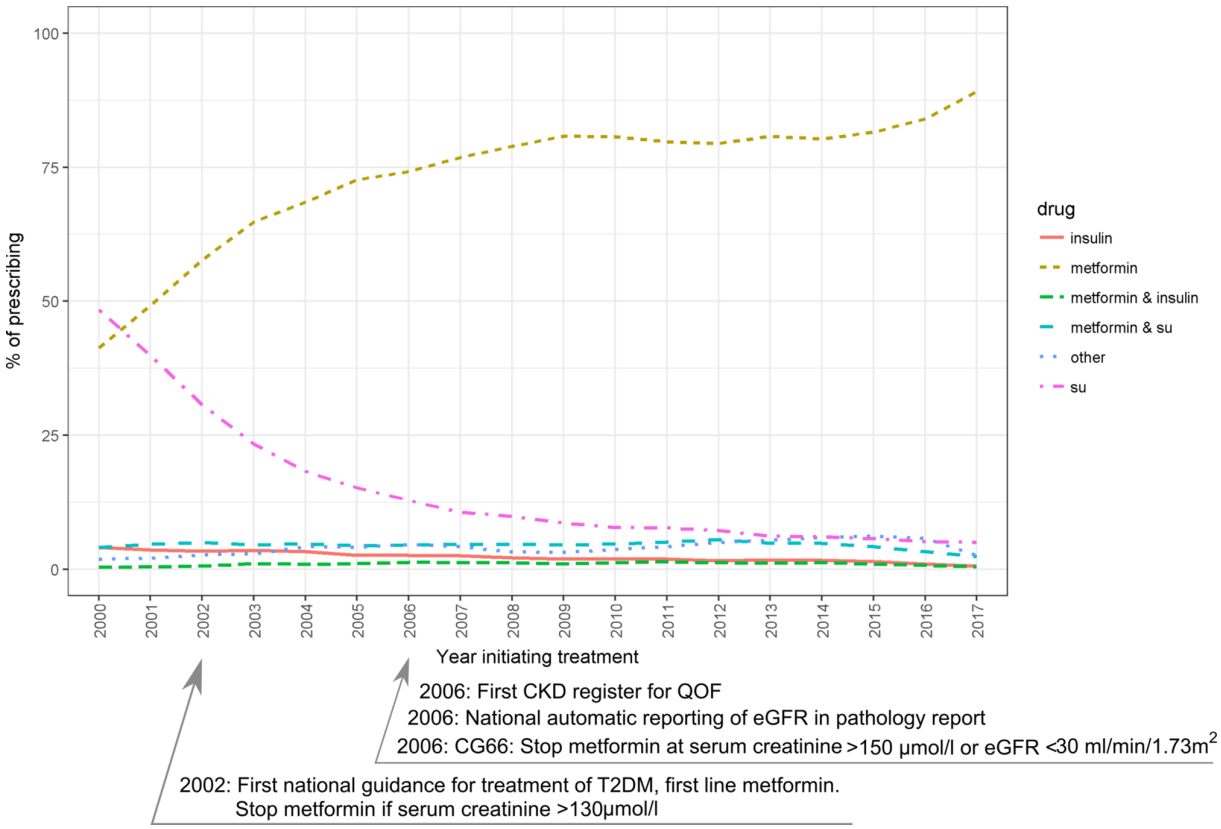

Figure 3 Drug prescribing at T2DM drug initiation 2000–2017.[14 21 22] CG, clinical guideline; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; QOF, Quality Outcomes Framework; SU, sulfonylurea; T2DM, type 2 diabetes mellitus.

the period and 13 988/280 241 (5%) started another drug option. Of this 5%, the most common drugs were insulin in combination with metformin (2850/13 988), TZD in combination with metformin (1405/13 988) or TZD alone (1393/13 988). A full list of combinations is provided in online supplementary table 1.

Temporal patterns of prescribing: treatment initiation

Patterns of treatment initiation drug prescribing changed over time (figure 3 and online supplementary table 2). In 2000, GPs prescribed SU monotherapy more often than metformin monotherapy but have increasingly prescribed metformin which now accounts for 89% (95% CI 88% to 90%) of drug initiations for T2DM. A small number of people in our drug initiation cohort start treatment on insulin therapy and this declines over time. Prescribing of insulin fell from 4% in 2000 to 0.58% in 2017.

Prescribing among people with reduced renal function

We found 145 822/280 241 (52%) people with eGFR measured in the 540 days prior to initiating drug therapy. Of these 1135/145 822 (1%) had an eGFR ≤30 mL/min/1.73 m^2 and 5395/145 822 (4%) had a serum creatinine ≥130 µmol/L. Among people with an eGFR ≤30 mL/min/1.73 m^2 the most common drug for initiating treatment was an SU at 58% (659/1135) of total prescribing from 2000 to 2016. Prescribing of metformin as the first drug in this group fell steadily from 29% (95% CI 28% to 30%) in 2000 to 9.5% (95% CI 9% to 10%) in 2016. Since being licensed in 2007, prescriptions for DPP4is as initial therapy for this subgroup have steadily increased to 33% (95% CI 32% to 34%) in 2016. Full details of prescribing are supplied in online supplementary table 3. A comparison of initiation drug prescribing between the current and earlier guidance on renal function is presented in online supplementary figure 1.

Temporal patterns of prescribing: first stage of drug intensification

Of the individuals who started metformin monotherapy, we identified 105 348/277 232 (38%) people who started on metformin and then received a second class of T2DM drug. Of these, 79 941/105 348 (76%) were prescribed metformin in the 60 days after the new drug prescription, indicating treatment intensification rather than switching. Among these 79 941 people, the drugs prescribed at the first stage of drug intensification have changed over the period of the study (figure 4).

In 2000, SU prescribing dominated drug choices at the first stage of intensification, accounting for 87% (95% CI 84% to 90%) of new drug intensifications. By 2017, this fell to 30% (95% CI 25% to 35%). Between 2000 and 2006, there was a rise in the use of TZD class prescribing, but after

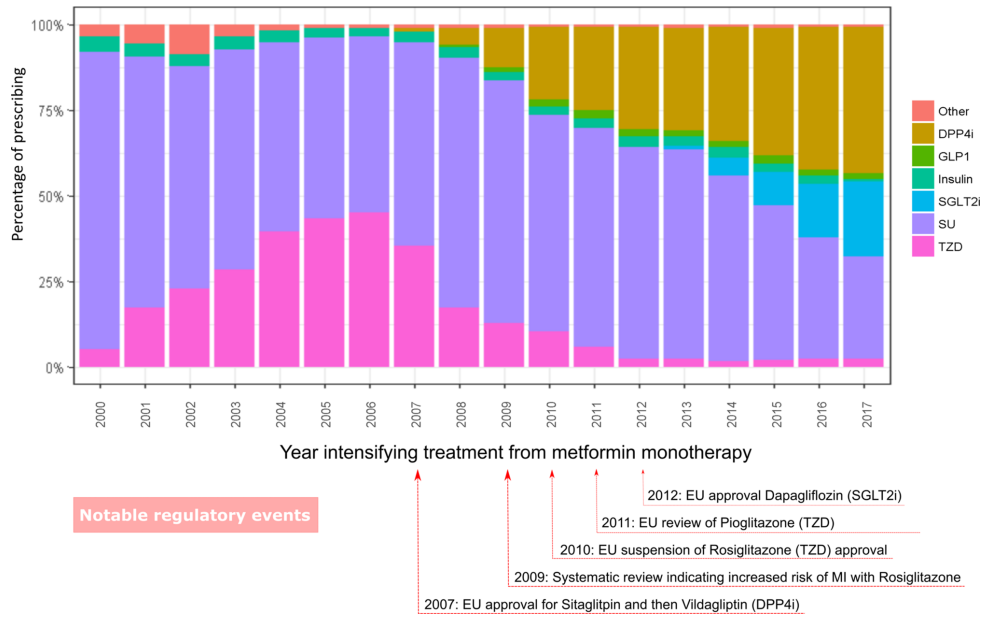

Figure 4 First-stage intensification prescribing as a percentage of total prescribing 2000–2017.[31 35 36] DPP4i, dipeptidyl peptidase-4 inhibitor; EU, European Union; GLP1, glucagon-like peptide-1; MI, myocardial infarction; SGLT2i, sodium/glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinediones.

2006, TZD use fell. In 2017, TZD prescribing accounted for only 2% (95% CI 0% to 8%) of prescribing, compared with a peak of 45% (95% CI 43% to 47%) in 2006. Prescribing of two new drug classes, DPP4is and SGLT2is increased since their introduction in 2007 and 2012, respectively. In 2017, new prescriptions for DPP4is accounted for 42% (95% CI 38% to 47%) of first stage of intensification drug choices. SGLT2i prescribing is rising, accounting for 22% (95% CI 17% to 27%) of new drug intensifications in 2017 (online supplementary table 4). Other than insulin (about 21 months) the other drugs were all started after a similar time period following metformin monotherapy (around 3–3.7 years) (online supplementary table 5).

REGIONAL DIFFERENCES

Prescribing practice differs between countries within the UK (figure 5, online supplementary table 6). For 2013–2017, GPs in Wales and Northern Ireland prescribed DPP4is in 45% (95% CI 42% to 48%) and 46% (95% CI 41% to 51%) of intensifications whereas in Scotland and England GPs prescribed DPP4is in just 30% (95% CI 26% to 34%) and

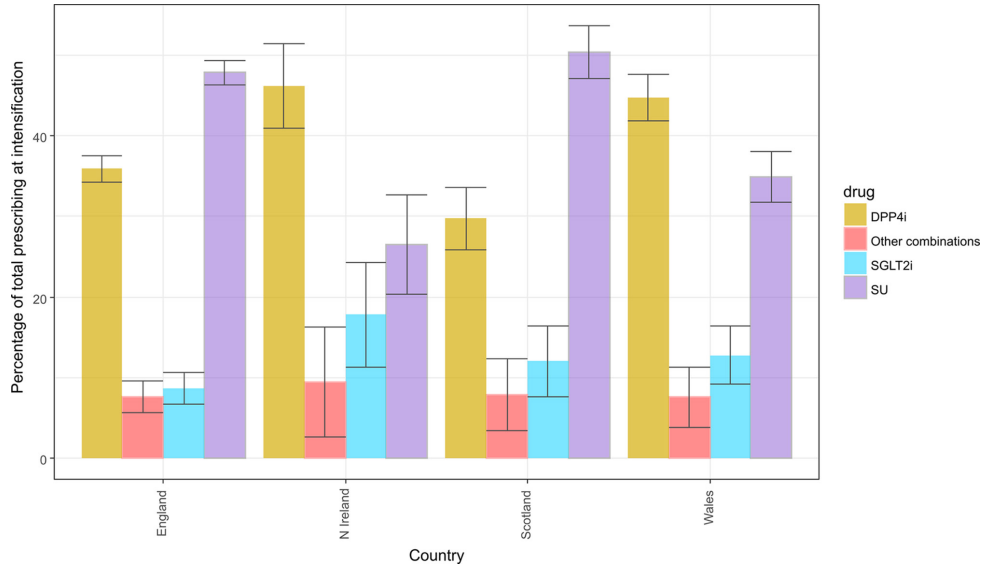

Figure 5 Proportions of patients at first-stage intensification prescribed a DPP4i, SU, SGLT2i and other drugs, by country, 2013–2017. DPP4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium/glucose cotransporter-2 inhibitor; SU, sulfonylurea.

36% (95% CI 34% to 38%) of patients intensifying treatment. GPs in Northern Ireland prescribed SGLT2is in 18% (95% CI 11% to 24%) of intensifications compared with 13% (95% CI 9% to 16%) in Wales, 12% (95% CI 8% to 16%) in Scotland and 9% (95% CI 7% to 11%) in England. We also found marked heterogeneity of prescribing practice across CCG groupings (online supplementary figure 2).

DISCUSSION

Our results show that prescribing of metformin has increased and prescribing of SUs has fallen at drug initiation for T2DM between 2000 and 2017, and shows increasing accordance with recommendations from national and international guidelines. In patients with an eGFR ≤30 mL/min/1.73 m^2 the most commonly prescribed initiation drug class was SUs until 2015, but since then DPP4is are more commonly prescribed. Of note, we found that approximately 1 in 10 people are prescribed metformin despite an eGFR ≤30 mL/min/1.73 m^2. Prescribing patterns at the first stage of drug therapy intensification have also changed, with prescribing of SUs and TZDs falling, while that of newer drug classes has risen. By 2017, the most commonly prescribed addition to metformin was a DPP4i. Prescribing practice differs by country within the UK. We identified large differences in prescribing practice between countries in the UK, with Northern Ireland and Wales prescribing both DPP4is and SGLT2is more commonly than in England or Scotland. We also show large variations in prescribing practice between CCGs.

Our large study uses data from a source of population representative primary care records from across the UK to provide great insight into real-world clinical practice from 2000 to 2017. We have attempted to improve direct comparability by developing cohorts that reflect distinct stages of the management of patients with T2DM, rather than examining total prescribing. We have been able to characterise renal function prior to drug initiation for the majority of patients to explore changing concordance with prescribing recommendations.

However, there are limitations to this analysis. We do not know if the prescribing was initiated in primary or secondary care. In the absence of wider demographic features about the CCGs such as age, socioeconomic status or ethnicity distributions we cannot explore factors that might drive variation in prescribing. For some patients, more recent eGFR measures may have been available to the prescribing GP in letters or discharge summaries from secondary care, while the result available to us from serum creatinine tests could have been measured during a previous acute illness. This misclassification may in part explain why, even in recent years, nearly 10% of patients appear to initiate treatment with metformin despite levels of renal function that should have contraindicated its use. We have not analysed drug intensification patterns for patients who did not initiate treatment with a period of metformin monotherapy although this is a small minority over recent years. We may have included a proportion of patients with T1DM, both those who commenced treatment with insulin, and those who started on drug therapy but were later reclassified. However, people commencing insulin accounted for only 2% of drug initiations over the whole period so this is unlikely to have a substantial impact on our results. Finally, since our definition of intensification was based on receiving a further metformin prescription, we may have misclassified some patients as switching from metformin monotherapy rather than intensifying treatment. For example, we will have excluded some patients who died after intensifying treatment before receiving a further metformin prescription.

The prescribing trends we identified are in keeping with a study completed using a different source of UK primary care data that examined prescribing up to 2013.[23] International comparisons also show similar trends with falls in SU prescriptions and increases in metformin use, accounting for 68% of treatment initiations in Italy in 2012, 77% in the USA in 2016, while our estimate was 84%.[3 24]

Our work has also highlighted an increase in prescribing of DPP4is for treatment intensification, similar to findings in the UK and the USA.[23 25] The additional period to 2017 covered by our analysis shows that these trends continued, with additional growth in SGLT2i prescribing.

Our results are also consistent with data from OpenPrescribing, a website that allows access to absolute numbers of near real-time GP prescriptions.[26] OpenPrescribing shows increased prescribing of DPP4is and SGLT2is but does not distinguish prescribing at different stages of treatment as we present here.

In relation to prescribing for patients with reduced renal function, our work mirrors prescribing trends from a recent US study that described prescribing over time in people with CKD, in particular the increasing use of DPP4is.[27] Our finding that metformin continues to be prescribed for patients with T2DM and severely impaired renal function echoes work from France which found that for a cohort of people with reduced renal function prescribed metformin, the prescription was against contraindications in 49% of cases, and Italy where 15% of participants with an eGFR <30 mL/min/1.73 m^2 were still prescribed metformin.[28 29]

Encouragingly, we have found that prescribing at initiation of drug treatment for T2DM largely follows national guidelines and concordance has improved over time. We have highlighted that uptake of new drugs at the first stage of intensification has increased rapidly over recent years with marked regional variation suggesting factors outside of clinical indication may be important; guidance from local bodies to CCGs, drug company marketing, local secondary care practice and patient demand may all influence prescribing.[30] Growing evidence that SGLT2is may offer long-term benefits for prevention of cardiovascular disease, results not previously seen for other treatments, may also have influenced prescribing, although guidelines have not yet been altered.[20 31] Increasing use of patented drugs will drive up prescribing costs, an issue of concern as drugs for diabetes now account for

approximately 10% of the total cost of National Health Service primary care prescribing spending.[32]

In conclusion, our results showed marked changes in prescribing for T2DM since 2000 with large increases in prescribing of the new agents. There is substantial variation between regions and CCGs, despite no national guidance towards prescribing of specific agents. The factors underlying choice of drug options for the first stage of intensification are unexplained, and whether drug choice affects future clinical outcomes needs to be determined.

Contributors SVW, ID, LS, HSF and LT were responsible for developing the research question. SVW, LT and ID completed the data analysis and summarised the results. SW drafted the manuscript. All authors (SVW, ID, HSF, DF, AP, LS, LT) have read, commented on and approved the final manuscript.

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Competing interests SVW is funded by a GSK PhD scholarship. HSF is an employee of and holds shares in GSK. ID is funded by, holds stock in and has consulted for GSK. LS is funded by grants from Wellcome and has received grants from MRC and NIHR, grants and personal fees from GSK, grants from BHF, grants from Diabetes UK, outside the submitted work, and is a Trustee of the British Heart Foundation. AP reports personal fees from Novo Nordisk, and personal fees from Boehringer and Lilly, outside the submitted work. DF reports personal fees from ACI Clinical for clinical trial adjudication, outside the submitted work.

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Ethics approval Health Research Authority Research Ethics Committee.

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4.4 Description of specific drugs within each class, and changes over time

4.4.1 Drug agent prescribing according to drug class

Paper 2 provided a summary of the changing prescribing practice according to diabetes drug class. In this thesis, I have grouped products under drug classes because NICE guidance only references classes and does not specify which drug to use. However, many clinical trials investigated a single agent. This summary describes drug prescribing according to the agent within each class.

Table 4.1 describes the frequency of drug agent prescribing according to product class. This is restricted to individuals eligible for inclusion in the study presented in **Chapter 6**, at the first stage of treatment intensification.

Drug	Frequency	Percentage
Sulfonylurea	**5,010**	**100.00**
gliclazide	4,626	92.34
glimepiride	320	6.39
glipizide	54	1.08
glibenclamide	9	0.18
tolbutamide	<5	<0.1%
DPP4i	**4,434**	**100.00**
sitagliptin	2,348	52.95
linagliptin	941	21.22
saxagliptin	573	12.92
alogliptin	541	12.20
vildagliptin	31	0.70
SGLT2i	**1,187**	**100.00**
dapagliflozin	841	70.85
empagliflozin	202	17.02
canagliflozin	144	12.13
Total	**10,631**	

Table 4.1 Drug agent prescribed at first stage intensification according to drug class, for individuals eligible for inclusion in Paper 4, presented in Chapter 6

Of the DPP4i drug class, GPs prescribed sitagliptin to 53% of people in receipt of DPP4is, and 21% received linagliptin. For those prescribed SGLT2is, dapagliflozin was the drug most commonly prescribed (71%), followed by empagliflozin (17%) and canagliflozin was prescribed for only 12% of individuals. For the SU group, gliclazide was prescribed for 92% of the SU group and glimepiride prescribed in 6% of cases.

The EMPA-REG (123) study and the CANVAS (55) study are two highly cited studies that show positive effects of empagliflozin and canagliflozin on blood pressure, eGFR, BMI and HbA1c compared to placebo. However, over the period studied, representation of these two drugs is low in clinical practice. Dapagliflozin was the first SGLT2i introduced to the UK market at the end of 2012, which may have driven this.(122)

4.4.2 Changes in drug prescribing over time according to drug agent

Figure 4.1 shows the products prescribed for SU, DPP4i and SGLT2i drug classes, from 2000 to 2017. Since 2015, empagliflozin has been prescribed with increasing frequency compared to the older dapagliflozin. This increasing share of SGLT2i prescribing may be influenced by the EMPA-REG results published in 2015. In addition to clinical trials, factors such as local guidance, familiarity with drugs and communication with pharmaceutical companies may influence the uptake of new drug agents.

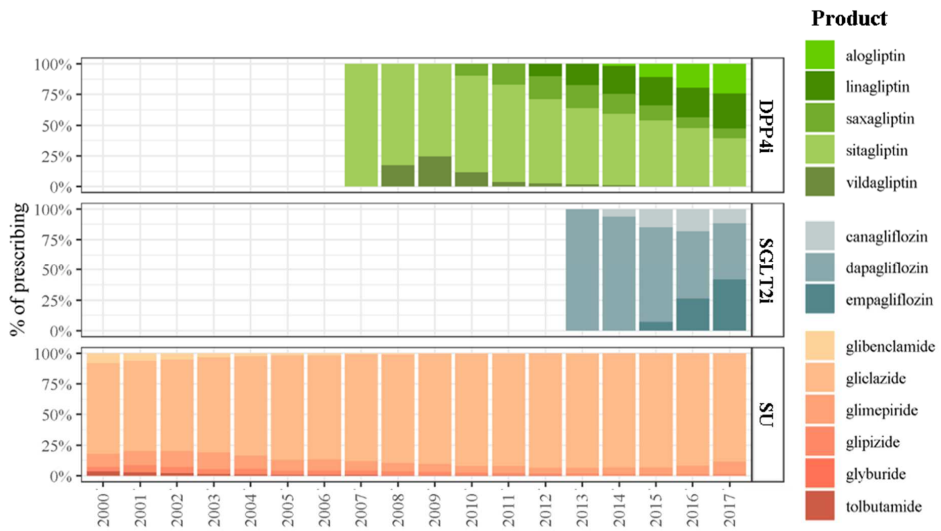

Figure 4.1 Product prescribing over time according to class of antidiabetic drug, for individuals eligible for inclusion in paper 4, chapter 6. According to drug class SGLT2i, DPP4i and SU.

Abbreviations: DPP4is: Dipeptidyl peptidase 4 inhibitors, SGLT2is: Sodium-glucose cotransporter-2 inhibitors, SU: Sulfonylureas

Over time, prescribing within the SU class has altered. Gliclazide is a second generation SU, associated with fewer hypoglycaemic events than glimepiride.(124) Small increases in the prescribing of gliclazide compared to glimepiride over recent years may have been driven by improved understanding of higher risks of hypoglycaemia, and the potential dangers of these events for the elderly, frail or those with reduced renal function.

In the DPP4i group, new drug agents account for higher proportions of DPP4i prescribing. GP prescribing of vildagliptin peaked in 2009 and by 2017, GPs appear to prescribe it only rarely. To validate these findings, I checked raw prescribing numbers on the OpenPrescribing website. OpenPrescribing showed low relative prescribing of vildagliptin in 2017 compared to sitagliptin (119,348 items for vildagliptin vs. 2,686,119 items for sitagliptin).(125) Low prescribing of vildagliptin may be driven by additional requirements to test liver function at three monthly periods during the first year of use, as hepatic dysfunction is a potential side effect.(126) These data suggest changing perceptions of drugs, both at the class level, and within drug classes. The full drug code list used in this follow-up work is presented in **Appendix 4**.

5 Chapter 5: Factors associated with choice of intensification treatment for type 2 diabetes mellitus after metformin monotherapy: a cohort study in UK primary care (Paper 3)

Chapter summary

- In the previous chapters we have seen that GPs are increasingly prescribing new drugs, the DPP4is and the SGLT2is, to intensify treatment after metformin monotherapy.
- National Guidance does not direct GPs as to which of the drug options to choose, despite each drug class exerting glucose lowering effects in different ways, and with different risk profiles and restrictions on their use. It is not known what factors influence GPs choosing drug classes.
- Therefore, in this chapter I discuss **Paper 3** that investigates associations between patient-level factors and prescribing practice of GPs at the first stage of treatment intensification.
- The study shows that both clinical and non-clinical patient characteristics independently predict prescribing of newer drug options. Obese people were more likely to be prescribed SGLT2is (OR: 5.6, 95% CI: 3.9, 8.1) and DPP4is (OR: 1.7, 95% CI: 1.5, 2.0) compared to SUs.
- Ethnicity and lower socioeconomic status were associated with reduced use of newer drug options. People of South Asian ethnicity had smaller odds of receiving SGLT2is compared to SUs, with an odds ratio of 0.6 (95% CI: 0.4, 0.9).

5.1 Introduction to Paper 3 (Patient level factors associated with prescribing)

Given the findings from **Paper 2 (Study of prescribing trends)** that drug choice at initiation is associated with renal function, and that prescribing practice differs according to region, the aim in **Paper 3 (Patient level factors associated with prescribing)** was a more thorough investigation of which patient factors were associated with drug treatment decisions. Systematic differences in the way GPs prescribe drugs may introduce bias to outcome studies. If one drug class is used only in people with very poor HbA1c, confounding by indication will mean that effect estimates comparing choice of treatment on HbA1c as an outcome may be non-causally associated with the treatment choice. A full understanding of the differences between individuals prescribed each treatment option is therefore imperative prior to outcomes research.

The following paper was published in Clinical Epidemiology. It describes clinical, demographic and social patient characteristics associated with each of the commonly prescribed intensification options used in the UK: SUs, DPP4is and SGLT2is.

There was substantial missingness for some variables of interest. Rather than restricting the analysis to only individuals without missing data (a complete-case analysis) I applied multiple imputation in the primary analysis. Complete case analysis will give unbiased estimates if the missing data is missing completely at random (MCAR), or missingness is not associated with the outcomes. This may be a reasonable assumption to make; the outcome of interest in **Paper 3** is prescribing choice. However, even under these circumstances, complete-case analysis will result in less efficient analyses as data from a large proportion of eligible individuals is discarded.(127)

Multiple imputation, assumes that missing data is missing is random (MAR). Under the assumption of MAR, the probability that the data is missing, depends on observed data.(128, 129)

Then, to estimate the odds of receiving each drug of interest I applied multinomial logistic regression with drug prescribing as the outcome and a range of patient characteristics as covariates. Multinomial regression is an extension of logistic regression that allows the outcome variable to have more than two levels, in this case a nominal three level outcome (SU, DPP4i or SGLT2i).(130) The SU group was the referent category as it was the largest group.

We found associations between drug options and both clinical and non-clinical characteristics. Some associations were unexpected, and not explained by clinical need. These findings suggest disparity in treatment, and channelling of new drugs to more privileged sections of society. Channelling is a type of selection bias that influences prescribing of new drugs to specific subgroups of the populations for reasons such as perceived improved safety. Channelling can result in new drug options being reserved for the highest (or lowest) risk groups. Channelling can therefore create bias by creating an association between baseline patient characteristics and future outcomes.(131)

It is possible that other factors may drive this disparity such as patient preference, practice-level differences, and local guidance but we could not explore these possibilities with the data available. This study provided crucial information for the design of the cohort study presented in **Chapter 6**. The study highlighted evidence of differential prescribing, and identified baseline factors that were important to account for when addressing confounding using propensity scores.

The supplementary files associated with the paper are provided in **Appendix 5**. These include a description of the drugs prescribed at the first stage of intensification other than SUs, DPP4i and SGLT2is and the results of sensitivity analyses to address the assumptions made in the primary analyses. Following the paper, in **Section 5.4**, I have provided further details of one of the sensitivity analyses. It shows the impact of the inclusion criteria that ensured people were intensifying treatment rather than switching treatment. As discussed earlier, this criterion relied upon information 'from the future' being used to inform inclusion and raises the possibility of immortal time bias.

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SECTION A – Student Details

Student	Samantha Wilkinson
Principal Supervisor	Laurie Tomlinson
Thesis Title	Prescribing trends, utilisation and comparative effectiveness of antidiabetic drug therapies prescribed in UK primary care

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Clinical Epidemiology		
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ORIGINAL RESEARCH

Factors associated with choice of intensification treatment for type 2 diabetes after metformin monotherapy: a cohort study in UK primary care

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Purpose: To understand the patient characteristics associated with treatment choice at the first treatment intensification for type 2 diabetes.

Patients and methods: This is a noninterventional study, using UK electronic primary care records from the Clinical Practice Research Datalink. We included adults treated with metformin monotherapy between January 2000 and July 2017. The outcome of interest was the drug prescribed at first intensification between 2014 and 2017. We used multinomial logistic regression to calculate the ORs for associations between the drugs and patient characteristics.

Results: In total, 14,146 people started treatment with an intensification drug. Younger people were substantially more likely to be prescribed sodium-glucose co-transporter-2 inhibitors (SGLT2is), than sulfonylureas (SUs): OR for SGLT2i prescription for those aged <30 years was 2.47 (95% CI 1.39–4.39) compared with those aged 60–70 years. Both overweight and obesity were associated with greater odds of being prescribed dipeptidyl peptidase-4 inhibitor (DPP4i) or SGLT2i. People of non-white ethnicity were less likely to be prescribed SGLT2i or DPP4i: compared with white patients, the OR of being prescribed SGLT2i among South Asians is 0.60 (95% CI 0.42–0.85), and for black people, the OR is 0.54 (95% CI 0.30–0.97). Lower socioeconomic status was also independently associated with reduced odds of being prescribed SGLT2is.

Conclusion: Both clinical and demographic factors are associated with prescribing at the first stage of treatment intensification, with older and non-white people less likely to receive new antidiabetic treatments. Our results suggest that the selection of treatment options used at the first stage of treatment intensification for type 2 diabetes is not driven by clinical need alone.

Keywords: drug prescriptions, diabetes mellitus, type 2, hypoglycemic agents, primary health care, practice patterns, physicians

Introduction

Current UK and international guidelines endorse metformin as the first-line treatment for most patients with type 2 diabetes.[1–4] In the UK, if further treatment is needed, National Institute for Health and Care Excellence (NICE) guidance suggests the addition of sulfonylureas (SUs), sodium-glucose co-transporter-2 inhibitors (SGLT2is), dipeptidyl peptidase-4 inhibitors (DPP4is), and thiazolidinediones (TZD) that have different risk profiles and restrictions.[1] The most commonly prescribed drug options are SUs, DPP4is, and SGLT2is.[5] Two of these drug classes have been available only recently, DPP4is since 2007 and SGLT2is since 2013.[1–4] Another drug class recommended by NICE at this stage of treatment are the TZDs; however, prescribing of TZDs has fallen substantially over recent years and is now rarely used at the first stage of treatment intensification in the UK.[5,6]

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At present, guidelines do not present evidence of superiority for any of these first-stage intensification drug choices. The factors influencing prescribing are not known but may include reported adverse events, growing familiarity with new agents, evidence from clinical trials, and influence of pharmaceutical companies.[6,7] Therefore, our aim was to examine the patient characteristics associated with the class of drug prescribed within primary care in the United Kingdom National Health Service (NHS). To ensure comparability and to reflect recent changes in practice, we focused only on commonly used drug classes at the first stage of drug intensification for type 2 diabetes: SUs, DPP4is, and SGLT2is, between 2014 and 2017.

Materials and methods

Study design and setting

This noninterventional study used data from the UK Clinical Research Datalink (CPRD), a database of pseudonymized primary care health data broadly representative of the UK population. CPRD data include demographic and lifestyle factors, prescribing records, clinical diagnoses test records, and referrals to secondary care. Data are regularly audited to ensure quality.[8] In the UK, most people with type 2 diabetes are managed in primary care with specialist input only for those with complications or very poor glycemic control.[1]

Participants, exposures, and outcomes

We identified all individuals aged 18 years and over. Although type 2 diabetes is typically associated with people over the age of 40 years, we chose to include younger patients since the age of diagnosis is decreasing over time, and earlier onset is associated with poorer patient outcomes.[9,10] We included only patients registered at the practice for 12 months without treatment for type 2 diabetes in order to restrict the cohort to new users of type 2 diabetes drugs, and to limit inclusion of patients with type 1 diabetes mellitus. We excluded women with type 2 diabetes and a history of pregnancy within 12 months of potential inclusion as prescribing guidelines recommend different drug regimens for pregnant and breastfeeding women.[11]

To be eligible, individuals must have initiated treatment with metformin monotherapy between 2000 and 2017. Metformin is the only drug recommended by NICE as a first-line drug treatment for type 2 diabetes unless contraindicated, usually for patients with estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2.[1,12]

Outcomes

We investigated the drug prescribed at the first stage of intensification as our study outcome and focused on three classes of drug recommended by clinical guidelines: SU, DPP4i, and SGLT2i. TZDs are now infrequently prescribed for new users, so we did not investigate this class of drug as an outcome.[5] As SGLT2is only became available recently, we limited the period to individuals who commenced treatment after 2013.[5] Insulin is not recommended at the first stage of drug intensification so a prescription for insulin may suggest a change of diagnosis to type 1 diabetes mellitus, or very poor glycemic control. We therefore did not include it as an outcome but provide a descriptive analysis of individuals prescribed insulin in the Supplementary files. Intensification of treatment was defined as prescriptions for type 2 diabetes drugs other than metformin after the day of metformin initiation. To minimize misclassification from individuals switching drug regimens rather than intensifying treatment, we required that a further prescription for metformin was issued within 60 days of the first-stage intensification drug prescription (Figure 1).

Descriptive variables and covariates

We defined characteristics that we considered may influence prescribing choice based on clinical knowledge of type 2 diabetes, current treatment guidelines, and recommendations for individual drugs. We defined these covariates as those

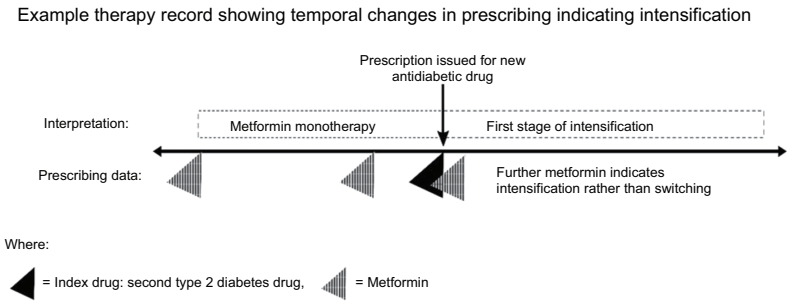

Figure 1 Diagram of identification of individuals at the first stage of intensification of treatment for type 2 diabetes from prescribing records.

recorded prior to the day the first-stage intensification drug was prescribed. For the regression analysis, we considered age, sex, body mass index (BMI), ethnicity,[13] socioeconomic status, smoking, hemoglobin A1c (HbA1c), eGFR,[14] albumin:creatinine ratio (ACR), indicators of microvascular disease, and number of days taking metformin prior to change. For all biochemical variables, we included only the last record of each covariate in the patient record prior to drug intensification, as we considered this was most likely to influence the prescribing clinician at the point of changing treatment. Comorbid conditions, cardiovascular disease (CVD), retinopathy,[15] prior amputations,[16,17] diagnoses for neuropathy,[18] proteinuric kidney disease, heart failure,[19,20] and blindness[16,20] were defined as present if they were recorded in the medical record on or prior to the date of drug intensification. We defined drug exposures (ACEI/ARB or statins) as any prescription in the year before baseline. Patient-level socioeconomic status was assigned with quintiles of index of multiple deprivation (IMD) scores that were collated in 2015 as the most recent available data.[21]

For HbA1c test results, all units were converted to mmol/mol.[1] We excluded values less than 20 mmol/mol (4.0%), or greater than 200 mmol/mol (20.4%) as invalid. Results older than 540 days were classed as "missing" since they were unlikely to represent current glycemic control. We classified HbA1c into three groups: ≤53 mmol/mol (7%), 54–74 mmol/mol, and ≥75 mmol/mol (9%) to fit with NICE intensification target guidance (guidance recommends a target of 53 mmol/mol with insulin if HbA1c rises to 75 mmol/mol).

We calculated eGFR using the last serum creatinine result within 2 years. We assumed all creatinine measures were isotope-dilution mass spectrometry (IDMS)-standardized and calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) equation.[14] We excluded ethnicity from the estimate of eGFR as General Practitioners (GPs) receive unadjusted eGFRs in laboratory reports. We grouped eGFR results as analogous to CKD stage: 0 to <60 mL/min/1.73 m^2, 60 to <90 mL/min/1.73 m^2, and ≥90 mL/min/1.73 m^2.

To classify proteinuria, we used diagnostic codes for proteinuric kidney disease and continuous measures of ACR. We considered patients to have ACR above the normal range if ACR test records had a positive qualifier, or where the value was greater than 3 mg/mmol. We created a count variable of microvascular disease markers that included a positive ACR test result, a diagnosis of retinopathy, a diagnosis of neuropathy, or a diagnosis of proteinuric kidney disease.[22] To calculate the daily dose of metformin prior to treatment change, we used the last metformin prescription prior to treatment change and calculated daily dose as the strength prescribed multiplied by the number provided each day. We included calendar year, split into 6 monthly periods, as a covariate to account for prescribing trends in the UK.[5] All codes used in this analysis are publicly available on the EHR data compass website: http://datacompass.lshtm.ac.uk/692/.

Statistical analysis

We describe the patients prescribed each drug (SU, DPP4i, SGLT2i) at first intensification according to clinical, demographic, and lifestyle factors. We then used multinomial logistic regression modeling to better understand the relationships between drug usage and baseline covariates.[23] The OR for the explanatory variables denotes the association between each variable and each drug class at first-stage intensification compared with SU (baseline treatment).

The aim of the multinomial models is not to predict drug choice, but to identify which variables might be important to clinicians prescribing drugs for first-stage intensification. Therefore, we did not aim to find the most parsimonious model but drew conclusions from a model with as many relevant covariates as possible while ensuring the model would converge.[24] A priori, we defined a wide range of factors that we expected to be important to clinical decision-making, including patient demographic information, clinical measures, comorbidities, and lifestyle measures. We examined variables with strong collinearity and selected the variables for inclusion that were most valid given the data available. For example, we chose retinopathy as a marker of microvascular disease as a sensitive and validated measure that is well screened for in primary care,[15] and CVD as a marker of macrovascular disease that is well recorded.[25] We found low numbers of people with reduced kidney function, so we used wide eGFR classes to avoid zero-count cells.

To handle missing data, we used multiple imputation with chained equations under the assumption of data being missing at random (MAR).[26] We generated 40 imputed datasets. We used predictive mean matching to model continuous variables to better account for non-normality than linear regression: imputed values were drawn from the nearest ten non-missing observations.[27] We modeled categorical variables using multinomial logistic regression and ordered categorical variables using ordinal logistic regression. For missingness in continuous variables, HbA1c, BMI, and eGFR, we imputed the variables on the continuous scale and then converted to categorical variables after imputation. The imputation models included all covariates in the analysis model, as well as auxiliary variables including dementia, heart failure, and blindness diagnoses.

Data extraction and processing of CPRD data were completed in Stata MP (version 14). All data analysis has been completed using Stata MP 14 and R version 3.4.1.

Sensitivity analyses

Patient-level IMD data are only available for practices in England, effectively excluding patients in other countries in the UK. Therefore, for our primary analysis, we did not include IMD to maximize the representativeness of the findings. In our first sensitivity analysis, we repeated the primary model for England, including patient-level IMD data to explore the impact of this on treatment intensification.

In addition, to examine the sensitivity of our results to the assumptions made, we conducted further sensitivity analyses. If the patient was censored or died in the 60 days after an alternate drug was prescribed, it is not known whether further metformin therapy was intended by the GP, and therefore these individuals could be mistakenly excluded as drug "switchers". Therefore, in a sensitivity analysis, we included all patients who died in this period. Finally, retinopathy represents only one microvascular complication associated with type 2 diabetes but multiple complications may independently influence prescribing. Therefore, we repeated the primary analysis, replacing retinopathy with a count of microvascular disease markers including a positive ACR test result, diagnosis of retinopathy, neuropathy, or proteinuric kidney disease.

Post hoc analyses

We observed a strong calendar time interaction in the logistic regression. We therefore repeated the analysis for each individual year 2014–2016 (excluding time as a covariate) and compared ORs of interest using forest plots.

Ethical and scientific approval

The research protocol was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines & Healthcare products Regulatory Agency Database Research (protocol number 16_267). The protocol was made available to journal reviewers. This study was also approved by the London School of Hygiene and Tropical Medicine Ethics Committee, reference 11923.

Data availability

All codes used in this analysis are publicly available on the EHR data compass website: http://datacompass.lshtm.ac.uk/692/; no further data sharing is possible.

Results

We identified 307,554 people who started antidiabetic treatment, between 2000 and 2017, of whom 280,241 people were aged 18 years and over, with no recent evidence of pregnancy. Of these, 204,238 (73%) initiated treatment with metformin monotherapy and 38,739 people received SU monotherapy (14%). Of those starting treatment with metformin monotherapy, we identified 79,941 (39%) that intensified treatment with any further antidiabetic drug. We then restricted this group to 14,149 individuals who intensified treatment between 2014 and 2017 to reflect only contemporary prescribing decisions. In our selected cohort, 44% (6,294/14,149) received SU, 37% (5,285/14,149) received DPP4i, 11% (1,488/14,149) received SGLT2i, and 8% (1,082/14,149) received insulin or other combinations (Table S1). In keeping with our decision to focus on SUs, DPP4i, and SGLT2is, only 2% (290/14,149) of the cohort were prescribed TZDs between 2014 and 2017. Full inclusions and exclusions are presented in the flowchart in Figure 2.

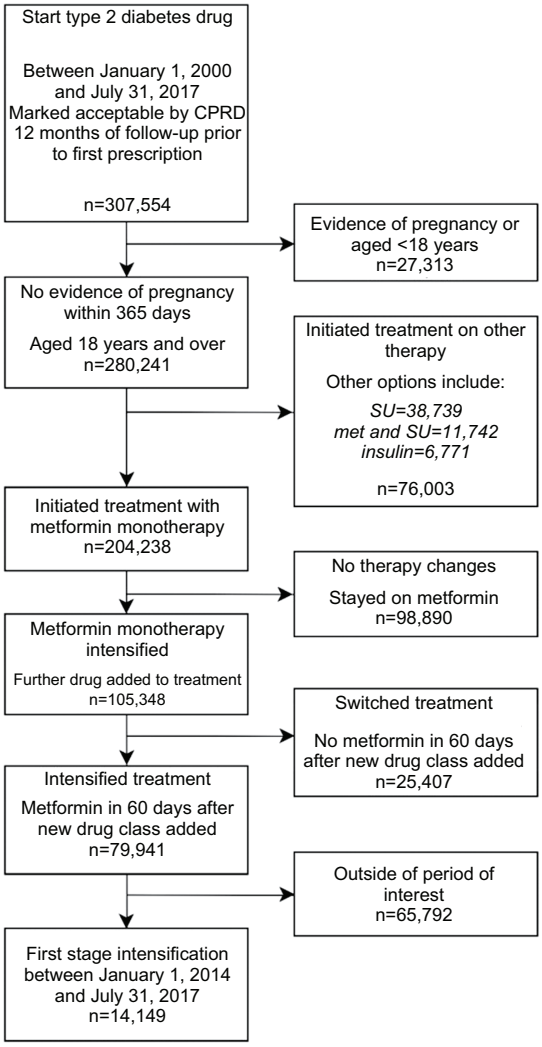

Figure 2 Flow diagram showing the creation of the study population and reasons for exclusion.
Abbreviation: CPRD, UK Clinical Research Datalink.

Table 1 Patient demographic and lifestyle factors, according to first-stage intensification drug prescribing

		SU N=6,294 Freq (%)[a]	DPP4i N=5,285 Freq (%)[a]	SGLT2i N=1,488 Freq (%)[a]
Age category (years)	<30	40 (0.6)	37 (0.7)	22 (1.5)
	30–39	224 (3.6)	168 (3.2)	71 (4.8)
	40–49	960 (15.3)	735 (13.9)	309 (20.8)
	50–59	1,719 (27.3)	1,442 (27.3)	554 (37.2)
	60–69	1,749 (27.8)	1,541 (29.2)	417 (28)
	70–79	1,140 (18.1)	1,010 (19.1)	106 (7.1)
	≥80	462 (7.3)	352 (6.7)	9 (0.6)
Gender	Female	2,561 (40.7)	2,093 (39.6)	614 (41.3)
BMI	Underweight/normal	742 (12)	411 (7.9)	33 (2.2)
	Overweight	1,970 (31.9)	1,488 (28.6)	236 (16)
	Obese	3,465 (56.1)	3,307 (63.5)	1,205 (81.8)
	Missing from complete cohort	117 (1.9)	79 (1.5)	14 (0.9)
Ethnicity	White	3,348 (84.3)	2,826 (89.2)	736 (92)
	South Asian	351 (8.8)	197 (6.2)	39 (4.9)
	Black	166 (4.2)	82 (2.6)	13 (1.6)
	Other	87 (2.2)	48 (1.5)	9 (1.1)
	Mixed	18 (0.5)	16 (0.5)	N<5
	Missing from complete cohort	2,324 (36.9)	2,116 (40)	688 (46.2)
Patient-level index of multiple deprivation	1 LEAST deprived	593 (17.1)	491 (19)	130 (20.7)
	2	634 (18.3)	473 (18.3)	132 (21.1)
	3	705 (20.4)	516 (20)	147 (23.4)
	4	802 (23.2)	520 (20.1)	120 (19.1)
	5 MOST deprived	729 (21.1)	581 (22.5)	98 (15.6)
	Missing from complete cohort	2,831 (45)	2,704 (51.2)	861 (57.9)
Alcohol status	Nondrinker	1,000 (16.5)	669 (13.1)	171 (12)
	Ex-drinker	879 (14.5)	757 (14.8)	207 (14.5)
	Current drinker	4,178 (69.1)	3,699 (72.2)	1,052 (73.6)
	Missing from complete cohort	237 (3.8)	160 (3)	58 (3.9)
Smoking status	Nonsmoker	2,386 (38)	1,968 (37.3)	589 (39.6)
	Current	1,041 (16.6)	813 (15.4)	238 (16)
	Ex-smoker	2,854 (45.4)	2,501 (47.3)	660 (44.4)
	Missing from complete cohort	13 (0.2)	N<5	N<5[c]
Days since first metformin prescription	Mean (SD)	1,182 (1,103)	1,320 (1,105)	1,137 (1,023)
Dose of previous metformin prescription (mg/day)	Mean (SD)	1,675 (525)	1,742 (484)	1,712 (470)
	Missing from complete cohort	2,165 (34)	1,757 (33)	529 (36)
HbA1c (mmol/mol)	Mean (SD)	80 (21)	73 (16)	76 (18)
	<53 (7%)[b]	182 (4.5)	146 (4.3)	34 (3.9)
	53–74	1,864 (45.7)	2,087 (61.5)	444 (51.4)
	>75 (9%)	2,030 (49.6)	1,164 (34.3)	386 (44.7)
	Missing from complete cohort	2,218 (35)	1,888 (36)	625 (42)
eGFR (mL/min/1.73 m^2)	Mean (SD)	87 (19)	85 (19)	94 (15)
eGFR category (mL/min/1.73 m^2)	<60	448 (10.7)	378 (11)	11 (1.2)
	60–89	1,694 (40.4)	1,457 (42.4)	314 (35.6)
	≥90	2,051 (48.9)	1,605 (46.7)	558 (63.2)
	Missing from complete cohort	2,101 (33.4%)	1,845 (34.9%)	605 (40.7%)
Proteinuric renal disease		159 (2.5)	101 (1.9)	23 (1.5)
Raised ACR		828 (28.9)	611 (24.9)	157 (24.9)
	Missing from complete cohort	3,431 (54.5)	2,836 (53.7)	858 (57.7)

(*Continued*)

Table 1 (*Continued*)

		SU N=6,294 Freq (%)[a]	DPP4i N=5,285 Freq (%)[a]	SGLT2i N=1,488 Freq (%)[a]
Neuropathy		408 (6.5)	326 (6.2)	70 (4.7)
Amputation		51 (0.8)	31 (0.6)	10 (0.7)
Retinopathy		1,061 (16.9)	1,018 (19.3)	227 (15.3)
Blindness		41 (0.7)	42 (0.8)	N<5
>1 sign of microvascular disease		2,073 (32.9)	1,721 (32.6)	416 (28)
Systolic BP (mmHg)	Mean (SD)	132 (14)	133 (14)	134 (14)
	Missing from complete cohort	20 (0.3)	11 (0.2)	N<5
CVD		878 (13.9)	744 (14.1)	150 (10.1)
Heart failure		103 (1.6)	57 (1.1)	14 (0.9)
ACEI or ARB prescription		3,342 (53.1)	2,973 (56.3)	828 (55.6)
Statin prescription		4,558 (72.4)	4,127 (78.1)	1,085 (72.9)

Notes: Numbers are N (%) unless otherwise stated. [a]Unless otherwise specified; % are of non-missing values, where missing categories are provided, percentage indicates percentage from the entire cohort. [b]HbA1c % represents HbA1c group according to the National Glycohemoglobin Standardization Program percentage. [c]Frequencies below five not stated as per Independent Scientific Advisory Committee for MHRA Database Research policy.

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ACR, albumin:creatinine ratio; ARB, angiotensin II receptor blockers; BMI, body mass index; CVD, cardiovascular disease; BP, blood pressure; DPP4i, dipeptidyl peptidase-4 inhibitors; HbA1c, hemoglobin A1c; SGLT2i, sodium-glucose co-transporter-2 inhibitors; SU, sulfonylurea; eGFR, estimated glomerular filtration rate.

Baseline characteristics of patients at point of type 2 diabetes drug intensification 2014–2017

Patient demographic and lifestyle factors for patients prescribed SUs, DPP4is, and SGLT2is are shown in Table 1. Details of patients prescribed insulin or other drug combinations are given in Table S2. The mean age of individuals intensifying treatment was 60 years, mean BMI was 33 kg/m^2, and mean eGFR was 87 mL/min/1.73 m^2. Individuals prescribed SGLT2is were younger, had higher BMIs, a higher representation of white people, and fewer people classed as more deprived. The DPP4i group had a higher proportion of obese people and white people compared with the SU group. Of the clinical factors, people prescribed SGLT2is had less impaired kidney function compared with people receiving SUs and DPP4i (Table 1). The prevalence of neuropathy, blindness, heart failure, dementia, and proteinuria was low, and similar, across the drug classes. The SGLT2i group had the lowest prevalence of CVD (10%) vs 14% in the SU and DPP4i groups.

Multinomial logistic regression

The results of the primary multinomial regression analysis are presented in Table 2. Age was associated with prescribing choice, with younger people substantially more likely to be prescribed SGLT2is than SUs. The OR for SGLT2i prescription for those aged <30 years was 2.47 (95% CI 1.39–4.39), compared to those aged 60–70 years, and there was a trend towards SU prescribing as age increases. SUs were more commonly prescribed for people with very poor glycemic control: among people with HbA1c >75, the OR for DPP4i prescription was 0.70 (95% CI 0.56–0.88) and that for SGLT2is prescription was 0.76 (95% CI 0.52–1.12) compared with that for SU prescription. For people with an eGFR >90 mL/min/1.73 m^2, the odds of receiving SGLT2is was 6.72 (95% CI 3.71–12.20) times greater than someone with an eGFR <60 mL/min/1.73 m^2. The presence of microvascular and macrovascular diseases was not associated with drug prescribing but both being overweight and obese were associated with greater odds of being prescribed both DPP4is and SGLT2is. Compared with white patients, the odds of being prescribed SGLT2i among South Asians was 0.60 (95% CI 0.42–0.85) and for black people the OR was 0.54 (95% CI 0.30–0.97). The odds of receiving DPP4i was also lower for South Asian and black people, 0.71 (95% CI 0.58–0.87) and 0.69 (95% CI 0.51–0.95), respectively. In the sensitivity analysis also including socioeconomic status, people from the two most deprived groups were also less likely to be prescribed SGLT2is (eg, OR 0.59 [95% CI 0.44–0.80] for the lowest fifth of IMD compared with the highest) while the findings for ethnicity were unchanged (Table S3). As we have shown previously, prescribing of DPP4i and SGLT2i drugs is increasing rapidly over time.[5]

Table 2 Fully adjusted ORs (95% CIs) for prescription of DPP4i or SGLT2i compared with SUs

Variable	SU, Ref	DPP4i, OR (95% CI)	SGLT2i, OR (95% CI)
N=	**6,294**	**5,285**	**1,488**
Age, years			
<30	1	1.37 (0.85–2.19)	2.47 (1.39–4.39)
30≤40	1	1.02 (0.82–1.28)	1.33 (0.97–1.82)
40≤50	1	0.98 (0.86–1.11)	1.27 (1.05–1.53)
50≤60	1	0.98 (0.88–1.08)	1.22 (1.04–1.42)
60≤70	1	1	1
70≤80	1	0.96 (0.86–1.08)	0.48 (0.37–0.60)
80 +	1	0.89 (0.75–1.06)	0.15 (0.07–0.29)
Gender			
Male	1	1	1
Female	1	0.92 (0.85–0.99)	0.99 (0.87–1.12)
HbA1c (mmol/mol)			
≤53	1	1	1
53–75	1	1.34 (1.07–1.67)	1.12 (0.77–1.63)
>75	1	0.70 (0.56–0.88)	0.76 (0.52–1.12)
eGFR (mL/min/1.73 m2)			
<60	1	1	1
60–89	1	1.05 (0.90–1.23)	5.86 (3.25–10.58)
>90	1	1.01 (0.86–1.18)	6.72 (3.71–12.20)
Time taking metformin (years)			
<1	1	1	1
1 to <3	1	1.27 (1.14–1.40)	1.40 (1.19–1.64)
>3	1	1.31 (1.18–1.44)	1.23 (1.05–1.44)
Cardiovascular disease (CVD)			
No CVD	1	1	1
CVD diagnosis	1	0.95 (0.85–1.06)	0.95 (0.77–1.16)
Retinopathy			
No retinopathy	1	1	1
Retinopathy diagnosis	1	1.09 (0.99–1.21)	1.02 (0.86–1.21)
BMI (kg/m^2)			
Normal/underweight	1	1	1
Overweight	1	1.30 (1.12–1.50)	2.22 (1.51–3.25)
Obese	1	1.70 (1.48–1.96)	5.61 (3.90–8.09)
Smoking status			
None	1	1	1
Ex	1	0.99 (0.90–1.08)	1.00 (0.87–1.15)
Current	1	0.94 (0.84–1.06)	0.81 (0.67–0.97)
Ethnicity			
White	1	1	1
South Asian	1	0.71 (0.58–0.87)	0.60 (0.42–0.85)
Black	1	0.69 (0.51–0.95)	0.54 (0.30–0.97)
Other	1	0.77 (0.52–1.14)	0.86 (0.39–1.88)
Mixed	1	1.14 (0.48–2.72)	2.08 (0.60–7.29)
Calendar time			
Early 2014	1	1	1
Late 2014	1	1.14 (1.00–1.29)	1.80 (1.38–2.36)
Early 2015	1	1.36 (1.20–1.53)	2.62 (2.04–3.37)
Late 2015	1	1.58 (1.38–1.80)	3.87 (3.01–4.98)
Early 2016	1	2.00 (1.75–2.28)	5.67 (4.42–7.27)
Late 2016	1	2.16 (1.86–2.51)	7.91 (6.13–10.20)
Early 2017	1	2.43 (2.06–2.86)	11.02 (8.46–14.36)

Note: Results of primary analysis, using multinomial logistic regression with multiple imputation to account for missing data.
Abbreviations: BMI, body mass index; DPP4i, dipeptidyl peptidase-4 inhibitors; HbA1c, hemoglobin A1c; SGLT2i, sodium-glucose co-transporter-2 inhibitors; SU, sulfonylurea; eGFR, estimated glomerular filtration rate.

Taking a complete case analysis approach to the model, or including individuals who were censored or died in the 60 days after prescribing of the intensification treatment for type 2 diabetes, produced no material differences from the primary analysis (Table S4). Redefining microvascular disease as a count of disease indicators also had no effect on the results (data not shown).

Post hoc analyses

Comparison of ORs for ethnicity for each individual year 2014–2016 (Figure S1) showed that for both South Asian and black people, the OR for receiving either SGLT2i or DPP4i was below 1.0 in every year, though for black patients the point estimate moves closer to 1.0 over time.

Discussion

We have identified clinical and nonclinical patient factors associated with drug prescribing between 2014 and 2017, a period when prescribing of the new drug classes, DPP4is and SGLT2is, rapidly increased.[5] Compared with SUs, SGLT2is were more commonly prescribed for younger people, for people who are overweight and obese, and for people who are white and of higher socioeconomic status. Findings for DPP4is are similar, although less marked. SUs are more commonly prescribed for patients with very poor diabetic control.

To our knowledge, this is the first analysis of factors associated with prescribing choice for the new type 2 diabetes drugs in the UK. Our findings reflect contemporary data, collected from a large primary care cohort from January 2000 to July 2017. We have identified patients starting additional treatments at a similar stage in their disease course, enabling direct comparability. However, there are limitations to this analysis. First, we may have misclassified some patients with type 1 diabetes, and as SGLT2is are used off-label as an adjunct therapy, this could in part explain our findings of an association with prescribing for the youngest patients. However, we excluded patients who were prescribed insulin at intensification, and required that metformin was re-prescribed after drug intensification, so any degree of misclassification is likely to be minimal. Second, drug prescribing may be influenced by local prescribing guidance such as preapproval restrictions issued by clinical-commissioning groups (CCGs).[28] In turn, CCGs may have varying proportions of residents of different ethnicities, so this again may influence our findings related to ethnicity and, similarly, to socioeconomic status. Restrictions related to maintaining anonymity of the data limit this level of data analysis. Third, we used prescribing data collected from primary care and we do not know which prescriptions were initiated in secondary care or specialist community care. Individuals intensified in specialist care environments may be more likely to receive newer drug options, which their GP then continues in primary care. Therefore, factors leading to inequity of access to new medications may occur by variation in who is referred to secondary care but we could not address this in our analysis. Finally, due to low numbers, we did not examine the characteristics associated with prescribing of TZDs, although these are a comparable choice in current prescribing guidance. Following a number of issues including concern about increased risk of heart failure and the 2011 MHRA warning of bladder cancer risk associated with use of pioglitazone, the TZDs have been infrequently prescribed for new users.[5,29,30]

Of the clinical factors assessed, some of the associations are expected. DPP4is are widely accepted to be weight neutral, and SGLT2is may aid weight loss, whereas SUs are associated with weight gain.[2] This may in part explain the independent association of being overweight and obese with being prescribed the new drugs. We found no SGLT2i prescriptions used in people with eGFR <45 mL/min/1.73 m^2. This suggests that prescribing of SGLT2is is aligned with clinical guidelines and prescribing information which restrict SGLT2i prescribing when kidney function is low.[31] SUs are also prescribed to the patients with the poorest glycemic control. This may reflect NICE guidance that recommends SUs for patients with symptomatic hyperglycemia, or clinicians may perceive that SUs are more effective at reducing HbA1c compared with DPP4is and SGLT2is.[1,32]

Our findings that age, ethnicity, and levels of deprivation are associated with choice of treatment are in line with other evidence regarding factors that influence prescribing of new drugs.[33] Younger patients are known to receive newer drugs more, perhaps driven by patient information and expectations, or by concern that older patients are more likely to experience side effects. However, SUs may not be the most appropriate treatment choice for older people, given their higher risks for hypoglycemia.[33–36] Globally, higher income patients often receive newer and more expensive drugs due to their ability to pay more for treatment.[33] However, in our study, all individuals are under the care of the NHS, and hence the ability to pay should have no bearing on prescribing, yet level of deprivation is still an independent predictor of drug choice. South Asian and black people received newer drug options (DPP4is and SGLT2is) less often than white people. Disparity in diabetes treatment by ethnicity is well established.[37] However, our finding that this extends to prescribing of new treatments is novel. The reasons for these differences are likely to be complex and could include patient awareness of

new drug choices, language barriers, or practice-level differences which we were unable to investigate.

An additional finding of our study is the marked differences between the characteristics of people prescribed SGLT2i in routine clinical use compared with randomized trials. The mean age of participants prescribed SGLT2i in our study was 55 years compared with 63.2 years in CANVAS and 63.1 years in EMPA-REG.[38,39] In addition, 68% of people in CANVAS randomized to SGLT2i had a prior history of CVD, compared with 10% of people with coded CVD who received SGLT2i in routine care in our study. The reason for the preferential prescribing of these drugs to younger people without ischemic heart disease in routine clinical care, despite the evidence base generated among people with CVD or high cardiovascular risk, is unclear.

This study demonstrates that where there is a choice between well-established and more novel treatments for type 2 diabetes, both clinical and nonclinical factors are associated with prescribing. These include age, ethnicity, and socioeconomic status, suggesting there is disparity in care unrelated to clinical need. The patient characteristics of those taking the newer drugs vary markedly from those studied in clinical trials. The impact of these factors on the clinical outcomes of patients with type 2 diabetes in a diverse population is not yet understood.

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Author contributions

SW, LAT, IJD, HAS-F, EW, and LS conceived and devised the study, and SW analyzed the data. All authors contributed to the interpretation of the data. SW drafted the article and all authors (SW, IJD, EW, HAS-F, DF, AP, LS, LAT) reviewed and edited the manuscript, and approved the version to be published, and agree to be accountable for all aspects of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. LAT accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

Disclosure

SW is funded by a GSK PhD scholarship. HAS-F is an employee of and holds shares in GSK. IJD is funded by, holds stock in and has consulted for GSK. DF has consulted for clinical trial adjudication associated with oral hypoglycemia medications (ACI clinical), and consulted for Boehringer-Ingelheim. AP reports personal fees from NovoNordisk, Boehringer Ingleheim, and Eli Lilly outside of the submitted work. LS has received grants from GSK and has received grants from the Wellcome Trust, the the Medical Research Council, the National Institute for Health Research, the British Heart Foundation, and Diabetes UK outside of the submitted work and is a Trustee of the British Heart Foundation. LAT and EW have no relevant conflicts of interest to disclose in this work.

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5.4 Sensitivity analyses of cohort definition

As detailed in **Section 1.1**, only individuals for whom GPs prescribed a first stage intensification drug, followed by a further metformin prescription were eligible for this study. I considered people without a record of metformin following treatment intensification to be treatment switchers, and excluded them from the analysis. When GPs switch treatment after metformin, rather than add another drug alongside metformin, as recommended in NICE guidance, they are probably doing so because the patient is intolerant of metformin. Therefore, people who are switching are likely to be clinically different to people intensifying treatment.(18)

As outlined in **Section 1.1**, this criterion may lead to bias. To be included in the study people needed to survive long enough to receive a further prescription for metformin. Therefore, in supplementary analyses I repeated the analysis including people that died or were censored for other reasons (e.g. leaving a GP practice) in the 60 day window where I checked for further metformin prescribing, **Table 5.1**.

Variable	SU, Ref	DPP4i, OR (95% CI)	SGLT2i, OR (95% CI)
Age at baseline, years			
< 30	*1*	1.36 (0.85, 2.17)	2.48 (1.39, 4.40)
30-<40	*1*	1.01 (0.81, 1.26)	1.32 (0.97, 1.81)
40-<50	*1*	0.98 (0.86, 1.11)	1.27 (1.04, 1.52)
50-<60	*1*	0.98 (0.88, 1.08)	1.21 (1.04, 1.42)
60-<70	*1*	1	1
70-<80	*1*	0.96 (0.85, 1.08)	0.47 (0.37, 0.60)
80 +	*1*	0.88 (0.74, 1.04)	0.14 (0.07, 0.28)
Gender			
Male	*1*	1	1
Female	*1*	0.92 (0.85, 1)	0.99 (0.87, 1.12)
HbA1c at baseline (mmol/mol)			
< 54	*1*	1	1
54-75	*1*	1.41 (1.14, 1.73)	1.17 (0.79, 1.71)
75+	*1*	0.73 (0.59, 0.90)	0.79 (0.54, 1.16)
eGFR at baseline (ml/min/1.73m^2)			
< 60	*1*	1	1
60-89	*1*	1.05 (0.90, 1.23)	5.88 (3.29, 10.50)
90 +	*1*	1.02 (0.86, 1.21)	6.77 (3.75, 12.23)
Time taking metformin prior to intensification (years)			
< 1	*1*	1	1
1 to <3	*1*	1.26 (1.13, 1.40)	1.40 (1.19, 1.64)
> 3	*1*	1.30 (1.17, 1.43)	1.23 (1.05, 1.44)
Diagnosis of cardiovascular disease			
No CVD	*1*	1	1
CVD diagnosis	*1*	0.94 (0.84, 1.06)	0.95 (0.78, 1.16)
Diagnosis of retinopathy			
No retinopathy	*1*	1	1
Retinopathy diagnosis	*1*	1.09 (0.99, 1.21)	1.02 (0.86, 1.21)

Variable	SU, Ref	DPP4i, OR (95% CI)	SGLT2i, OR (95% CI)
BMI at baseline, kg/m^2			
Normal/underweight	*1*	1	1
Overweight	*1*	1.31 (1.14, 1.51)	2.22 (1.52, 3.26)
Obese	*1*	1.72 (1.50, 1.98)	5.66 (3.93, 8.17)
Smoking status			
None	1	1	1
Ex	1	0.98 (0.90, 1.07)	1.00 (0.87, 1.15)
Current	1	0.93 (0.83, 1.05)	0.80 (0.67, 0.96)
Ethnicity			
White	*1*	1	1
South Asian	*1*	0.70 (0.57, 0.86)	0.60 (0.42, 0.89)
Black	*1*	0.66 (0.49, 0.90)	0.55 (0.29, 1.06)
Other	*1*	0.78 (0.50, 1.24)	0.87 (0.40, 1.67)
Mixed	*1*	1.17 (0.55, 2.49)	2.05 (0.61, 6.91)
Calendar time			
Early 2014	*1*	1	1
Late 2014	*1*	1.13 (1.00, 1.29)	1.80 (1.37, 2.35)
Early 2015	*1*	1.35 (1.20, 1.53)	2.62 (2.04, 3.36)
Late 2015	*1*	1.58 (1.38, 1.80)	3.87 (3.01, 4.98)
Early 2016	*1*	2.00 (1.75, 2.29)	5.68 (4.43, 7.28)
Late 2016	*1*	2.17 (1.87, 2.52)	7.90 (6.12, 10.20)
Early 2017	*1*	2.44 (2.07, 2.88)	11.11 (8.53, 14.47)

Table 5.1 Results of sensitivity analysis for censoring criteria. **Includes individuals that died or were censored in the 60-day check window for further metformin prescribing.** *Abbreviations: DPP4is: Dipeptidyl peptidase 4 inhibitors, SGLT2is: Sodium-glucose cotransporter-2 inhibitors, SU: Sulfonylureas*

The result of the sensitivity analysis showed that including the censored individuals had almost no impact on the estimates compared to the primary analysis. Of the people that were excluded as being treatment switchers from the primary analysis, only 65 people were censored in the check period. This suggests that the potential for bias is very low.

For the people included in the primary analysis, approximately one third received further metformin on the same day as the treatment intensification prescription, and were therefore selected for inclusion without using information from the future. I found most follow-up metformin prescriptions within the duration of prescription of the index drug. For each of the drug classes that I focussed on in this study, sulfonylureas, DPP4is and SGLT2is, the timing of metformin co-prescribing was similar, **Table 5.2**.

Metformin prescription found:	**SU, n (%)**	**DPP4i, n (%)**	**SGLT2i, n (%)**
On the same day as index drug	1869 (29.7)	1666 (31.5)	472 (31.7)
Within duration of index drug	3696 (58.7)	3046 (57.6)	818 (55.0)
Within duration of index drug + 60 days	729 (11.6)	573 (10.8)	198 (13.3)
Total	**6294**	**5285**	**1488**

Table 5.2 Timing of metformin prescribing in the check period following treatment intensification, for individuals selected for inclusion in Paper 3.

Abbreviations: DPP4is: Dipeptidyl peptidase 4 inhibitors, SGLT2is: Sodium-glucose cotransporter-2 inhibitors, SU: Sulfonylureas

5.5 Addition of interaction term between age and ethnicity

To investigate whether there was a differential association between drug prescribing and ethnicity according to age, I have included a post hoc analysis. This analysis is a repeat of the primary analysis with the addition of an interaction term between age and ethnicity. I could not include the interaction in the same model as the primary analysis as it would not converge due to the limited sample size. Instead, I have used smaller categories of age and ethnicity. Point estimates for ethnicity appear largely similar to the primary analysis. The interaction terms between older and being of south Asian ethnicity suggests some interaction with age, however 95% confidence intervals are wide and inconclusive, **Table 5.3**. This model is underpowered to investigate the marginal effects of ethnicity on drug prescribing, for each age category.

Variable **N=**	**SU, Ref** **6294**	**DPP4i, OR (95% CI)** **5285**	**SGLT2i, OR (95% CI)** **1488**
Age, years			
< 40	*1*		
40-<60	*1*	0.93, (0.74, 1.18)	0.77, (0.57, 1.03)
60-<80	*1*	0.93, (0.73, 1.18)	0.50, (0.36, 0.68)
80 +	*1*	0.85, (0.63, 1.12)	0.09, (0.04, 0.20)
Gender			
Male	*1*		
Female	*1*	0.92, (0.85, 0.99)	0.98, (0.86, 1.11)
HbA1c (mmol/mol)			
≤53	*1*		
53-75	*1*	1.32, (1.06, 1.64)	1.09, (0.77, 1.56)
>75	*1*	0.69, (0.56, 0.86)	0.76, (0.53, 1.09)
eGFR (ml/min/1.73m^2)			
<60	*1*		
60-89	*1*	1.06, (0.90, 1.23)	6.47, (3.60, 11.63)
>90	*1*	1.01, (0.86, 1.19)	7.85, (4.29, 14.35)
Time taking metformin (years)			
<1	*1*		
1 to <3	*1*	1.27, (1.14, 1.41)	1.40, (1.20, 1.65)
>3	*1*	1.30, (1.18, 1.44)	1.22, (1.04, 1.43)
Cardiovascular disease (CVD)			
No CVD	*1*		
CVD diagnosis	*1*	0.95, (0.84, 1.06)	0.93, (0.76, 1.13)
Retinopathy			
No retinopathy	*1*		
Retinopathy diagnosis	*1*	1.09, (0.99, 1.21)	1.01, (0.85, 1.19)

Variable	SU, Ref	DPP4i, OR (95% CI)	SGLT2i, OR (95% CI)
BMI kg/m^2			
Normal/underweight	*1*		
Overweight	*1*	1.30, (1.13, 1.50)	2.32, (1.58, 3.40)
Obese	*1*	1.71, (1.49, 1.96)	5.96, (4.14, 8.59)
Smoking status			
None	*1*		
Ex	*1*	0.94, (0.84, 1.06)	0.82, (0.69, 0.99)
Current	*1*	0.99, (0.90, 1.08)	0.99, (0.86, 1.14)
Ethnicity			
White	*1*		
South Asian	*1*	0.82, (0.46, 1.47)	0.24, (0.06, 0.93)
Black	*1*	0.50, (0.14, 1.79)	0.41, (0.05, 3.07)
Other	*1*	0.90, (0.25, 3.20)	-
Calendar time			
Early 2014	*1*	1.14, (1.00, 1.29)	1.82, (1.39, 2.38)
Late 2014	*1*	1.36, (1.20, 1.54)	2.63, (2.05, 3.38)
Early 2015	*1*	1.58, (1.39, 1.81)	3.90, (3.04, 5.02)
Late 2015	*1*	2.00, (1.75, 2.28)	5.69, (4.44, 7.29)
Early 2016	*1*	2.16, (1.86, 2.51)	7.91, (6.13, 10.21)
Late 2016	*1*	2.44, (2.07, 2.87)	10.95, (8.41, 14.26)
Early 2017	*1*	1.14, (1.00, 1.29)	1.82, (1.39, 2.38)
Interaction			
S Asian * 40<60	*1*	0.89, (0.48, 1.65)	2.41, (0.58, 10.00)
S Asian * 60<80	*1*	0.80, (0.41, 1.55)	3.37, (0.81, 13.96)
S Asian * 80+	*1*	0.74, (0.21, 2.60)	-
Black * 40<60	*1*	1.07, (0.29, 3.91)	0.98, (0.12, 7.84)
Black * 60<80	*1*	1.82, (0.46, 7.16)	2.40, (0.26, 22.39)
Black * 80+	*1*	-	-
Other * 40<60	*1*	0.87, (0.23, 3.33)	-
Other * 60<80	*1*	0.95, (0.23, 3.87)	-
Other * 80+	*1*	1.67, (0.20, 14.19)	-

Table 5.3 Fully adjusted odds ratios (95% CIs) for prescription of DPP4i or SGLT2i compared to SUs. Results of extra analysis with interaction between ethnicity and age. Multinomial logistic regression with multiple imputation to account for missing data. *Abbreviations: SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4inhibitors, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, HbA1c: Hemoglobin A1c, eGFR: estimated Glomerular Filtration Rate, BMI: Body mass inde*

6 Chapter 6: Routine clinical use of SGLT2is, sulfonylureas or DPP4is to intensify metformin monotherapy: Changes in blood glucose, kidney function, blood pressure and weight in UK primary care (Paper 4)

Chapter summary

- Recent clinical trials have suggested that the new SGLT2i drug class may be beneficial for people with type 2 diabetes, for reducing long-term adverse cardiovascular and renal outcomes.
- Comparative evidence for the SU, SGLT2i and DPP4i drug classes is limited. The aim of this chapter is to compare changes in eGFR, HbA1c, BMI and systolic BP, for people prescribed SUs, DPP4i or SGLT2is to intensify metformin monotherapy.
- Results indicate differences between the drug options, most notably in changes in HbA1c and BMI. People prescribed SGLT2i showed decreases in BMI of 1.7 kg/m^2 (95% CI: 1.4, 2.1), the DPP4i group fell by 0.8 kg/m^2 (95% CI: 0.6, 1.0) but BMI in the SU group did not change, 0.2 kg/m^2 (95% CI: 0.0, 0.4).
- This chapter opens with a synopsis of the steps taken to develop propensity score matched cohorts to account for differences at baseline. I matched cohorts on baseline factors given findings from **Chapter 5**.
- After the paper, I present a summary of outcome rates for kidney function decline, cardiovascular disease, heart failure and urinary tract infection, comparing SUs to DPP4is and SGLT2is. The results show that data from the July 2017 extract of CPRD GOLD provided inadequate power to undertake a cohort study with hard clinical endpoints.

6.1 Selection of method for Propensity Score matching across more than two treatment groups

In **Paper 3**, I identified several important patient factors that were associated with prescribing of the three treatments, SU, SGLT2i and DPP4i. Some of these variables were likely to be also associated with the outcomes, inducing confounding by indication. One example was baseline kidney function. We showed that GPs only prescribed SGLT2is to people with higher kidney function (eGFR). Given that baseline eGFR will likely impact change in kidney function after the start of treatment, we needed to adjust for baseline level. This would ensure that people prescribed different drugs are exchangeable at baseline and therefore reduce confounding by indication.

In **Paper 4**, to achieve a balance in baseline characteristics and to limit confounding, I applied propensity score matching. This is a commonly implemented method to compare treatment groups. Where patients with certain clinical factors have a higher chance of receiving one treatment over another, and where these factors are associated with outcomes, confounding by indication is likely.(132) Propensity scores (PS) act as a balancing score that allow researchers to use baseline covariates to adjust for confounders.

Researchers using PS matching generally compare one treatment with another. Given that three drug options are commonly prescribed in primary care at the first stage of treatment intensification, comparison of three groups is of clinical interest for this study. However, the process of creating matched cohorts for more than two treatment groups is not well defined. Imbens et al. recommends the use of multiple multinomial logistic regression models to calculate the propensity score, but using the PS to create matched cohorts is uncommon.(133, 134) Instead, more often,

researchers apply these propensity scores in PS adjusted regression, PS weighted regression or PS stratification.(133, 134) In **Paper 4**, creating matched samples is preferable to other methods to adjust for baseline covariates, as the aim is to compare longitudinal changes in HbA1c, BMI, systolic BP and eGFR. Matched cohorts mean that treatment groups are balanced in terms of baseline covariates and so the treatment effect models will not require further adjustment. Moreover, interpretation of the outcome models will be similar to the RCTs, showing changes in means over time. A further challenge to the analysis of comparative changes for three different drug classes is the small number of SGLT2i-treated individuals compared to the older drug options DPP4is and SUs. An important aspect of the selected statistical model is to maximise the power of the study population by using as many individuals from the SGLT2i group as possible.

A recent paper approached the challenge of three-way PS-score matching, suggesting a 1:1:1 matching technique that identifies groups of three individuals with the similar PS.(135) However, the technique suggested allows only 1:1:1 matching. Where one treatment group has low numbers, as is the case when comparing SGLT2is to SUs and DPP4is, this technique would limit the study sample size. Other authors have applied approaches referred to as 'common referent' whereby propensity scores are estimated using logistic regression, using one treatment arm as the same referent group, then only including matched pairs where the referent group had matches across all treatment arms.(136)

In collaboration with Dr Elizabeth Williamson, a statistician at LSHTM I developed the following approach. Initially I used logistic regression to estimate propensity for prescription of SGLT2i for each treatment group, SU and DPP4i. I selected the

SGLT2i treated group as the referent because this category was the smallest treatment arm. Then, I used an iterative process to identify the optimum balance in terms of baseline covariates. To further achieve close matching at baseline for the covariate of interest; eGFR, HbA1c, systolic BP and BMI I applied additional exact-matching criteria for baseline measure. The 'exact measure' was achieved by grouping the baseline measure, for example, grouping baseline eGFR according to quintiles, and only selected individuals that matched to eGFR quintiles at baseline.

To improve the power of the study, as there were many more people treated with SUs and DPP4is than SGLT2is, I sought more than one match to each SGLT2i treated individual. To reflect the ratio of people treated with SUs and DPP4is, I sought five SU treated and four DPP4i treated individuals for each person treated with SGLT2is. To balance the contribution of each individual, where too few matches were found for a SGLT2i treated person, greater weights were given to the matches found. The steps taken to create the final matched sets are illustrated in **Table 6.1**.

After matching on propensity score I applied a linear mixed model to model changes in BMI, systolic blood pressure, eGFR and HbA1c after starting the drugs of interest. The equation for the linear mixed model is given for the eGFR regression below:

$$eGFR_{ij} = \gamma_0 + \gamma_1(DRUG_{ij} = 2) + \gamma_2(DRUG_{ij} = 3) + \gamma_3 WEEK_{ij} + \gamma_4 WEEK_{ij}^2 + \gamma_5 WEEK_{ij}^3 + \gamma_6(WEEKCAT_{ij} = 1) \times (DRUG_{ij} = 2) + \gamma_7(WEEKCAT_{ij} = 1) \times (DRUG_{ij} = 3) + \cdots + \delta_{0i} + \epsilon_{ij}$$

, for repeated eGFR measure j in patient i.

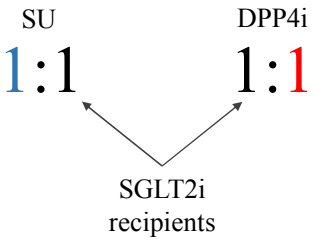
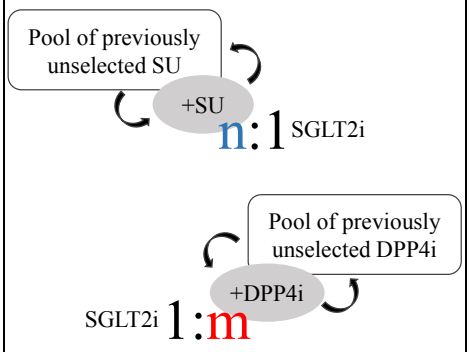
Step	Summary	Graphical representation
1	Estimate propensity score for SGLT2i in pairwise regressions. Identify nearest neighbour matches for each SGLT2i, without replacement. In both groups, SGLT2i vs Su and vs. DPP4i. Find 1 match for each SGLT2i.	
2	Try to find additional matches for the SGLT2i cases chosen in step one. Select further matches only from pool of SUs or DPP4i not previously selected. Aim for 5 SU matches for each SGLT2i and 4 DPP4i matches. Repeat process until enough matches found, or no further matches found within calliper.	
3	Discard SGLT2i treated individuals not found a match in the SU and DPP4i sets	n:1:m
4	Where 5:1:4 matching was not achieved; I assigned weights to under-matched groups.	Matched sets 5:1:4 Optimum matched set achieved Weights assigned 1/5 : 1 : 1/4 2:1:4 Too few matched achieved for SUs Weights assigned (1/5 x 5/2): 1 : 1/4 5:1:3 Too few matched achieved for DPP4is Weights assigned 1/5 : 1 : (1/4 x 4/3)

Table 6.1 Detail of steps taken to create propensity score matched sets of individuals prescribed DPP4is, SGLT2is or SU. The aim for number of matches, m and n, was five and four respectively to reflect the ratio of SU and DPP4i users compared to SGLT2i group.

Abbreviations: SU: Sulfonylureas, SGLT2is: Sodium-glucose cotransporter-2 inhibitors, DPP4is: Dipeptidyl peptidase 4 inhibitors

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SECTION A – Student Details

Student	Samantha Wilkinson
Principal Supervisor	Laurie Tomlinson
Thesis Title	Prescribing trends, utilisation and comparative effectiveness of antidiabetic drug therapies prescribed in UK primary care

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Diabetes, Obesity and Metabolism		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author on this paper. I participated by writing the protocol for the study, analysing the data and drafting the manuscript. My co-authors supported the work by advising on research design, analysis and commenting on drafts of the paper

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ORIGINAL ARTICLE

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Comparative effects of sulphonylureas, dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter-2 inhibitors added to metformin monotherapy: a propensity-score matched cohort study in UK primary care

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Abstract

Aim: To assess the comparative effects of sodium-glucose co-transporter-2 (SGLT2) inhibitors, sulphonylureas (SUs) and dipeptidyl peptidase-4 (DPP-4) inhibitors on cardiometabolic risk factors in routine care.

Materials and methods: Using primary care data on 10 631 new users of SUs, SGLT2 inhibitors or DPP-4 inhibitors added to metformin, obtained from the UK Clinical Practice Research Datalink, we created propensity-score matched cohorts and used linear mixed models to describe changes in glycated haemoglobin (HbA1c), estimated glomerular filtration rate (eGFR), systolic blood pressure (BP) and body mass index (BMI) over 96 weeks.

Results: HbA1c levels fell substantially after treatment intensification for all drugs: mean change at week 12: SGLT2 inhibitors: −15.2 mmol/mol (95% confidence interval [CI] −16.9, −13.5); SUs: −14.3 mmol/mol (95% CI −15.5, −13.2); and DPP-4 inhibitors: −11.9 mmol/mol (95% CI −13.1, −10.6). Systolic BP fell for SGLT2 inhibitor users throughout follow-up, but not for DPP-4 inhibitor or SU users: mean change at week 12: SGLT2 inhibitors: −2.3 mmHg (95% CI −3.8, −0.8); SUs: −0.8 mmHg (95% CI −1.9, +0.4); and DPP-4 inhibitors: −0.9 mmHg (95% CI −2.1,+0.2).

BMI decreased for SGLT2 inhibitor and DPP-4 inhibitor users, but not SU users: mean change at week 12: SGLT2 inhibitors: −0.7 kg/m^2 (95% CI −0.9, −0.5); SUs: 0.0 kg/m^2 (95% CI −0.3, +0.2); and DPP-4 inhibitors: −0.3 kg/m^2 (95% CI −0.5, −0.1). eGFR fell at 12 weeks for SGLT2 inhibitor and DPP-4 inhibitor users. At 60 weeks, the fall in eGFR from baseline was similar for each drug class.

Conclusions: In routine care, SGLT2 inhibitors had greater effects on cardiometabolic risk factors than SUs. Routine care data closely replicated the effects of diabetes drugs on physiological variables measured in clinical trials.

1 | INTRODUCTION

Type 2 diabetes mellitus is a leading cause of morbidity and mortality worldwide, resulting in one million deaths worldwide in 2017.[1] Drug treatments often provide benefits for glycaemic control and surrogate outcomes but, recently, clinical trials of sodium-glucose co-transporter 2 (SGLT2) inhibitors have shown substantial reductions in adverse cardiovascular and renal outcomes.[2-5] In these major outcome trials, SGLT2 inhibitors have been compared to placebo, contrasting with the way the drugs have been recommended for use in clinical practice: international guidelines have recommended SGLT2 inhibitors as an option to intensify glycaemic control after metformin monotherapy, but with sulphonylureas (SUs), thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists as alternate choices.[6,7]

The SGLT2 inhibitors work by inhibiting reabsorption of glucose in the proximal renal tubule and thus lowering blood glucose levels. As well as improved glycaemic control, this results in weight loss, blood pressure reduction and diuresis.[8] In clinical trials of SGLT2 inhibitors, patients in the active treatment arm have shown lower blood pressure and better glycaemic control compared to patients in the placebo arm.[2-5] There is limited evidence, however, that lower blood pressure or tighter diabetic control is associated with better cardiovascular outcomes[9,10]; therefore, it is not clear whether the improved clinical outcomes in SGLT2 inhibitor-treated patients are explained by improvements in known cardiovascular and renal risk factors, which might also occur for other drug classes in direct comparator trials, or whether other mechanisms exist.[11]

Observational studies have compared major outcomes in SGLT2 inhibitor users with those in people who have no additional treatment, and also with those in people using active comparator agents.[12-17] These studies also report substantial outcome benefits for SGLT2 inhibitor users but have been criticised for failing to adequately account for sources of bias and confounding, in particular, for the fact that SGLT2 inhibitors were prescribed to younger patients with fewer comorbidities.[18] Only few observational studies have examined the effects of first-line intensification drugs for type 2 diabetes on biological variables and these have mainly focused on the comparative effects of drug classes on glycaemic control.[19-21] The effects of SGLT2 inhibitor drugs on physiological variables, such as blood pressure, measured in routine care, and how these relate to the results observed within the standardized setting of clinical trials, are currently unknown.

The use of DPP-4 or SGLT2 inhibitors for first-stage intensification of control of type 2 diabetes has been increasing rapidly in routine clinical care over recent years, with wide variation in prescribing patterns.[22] There has been relative equipoise for choice of intensification drug offered by current clinical guidelines, and limited differences in the characteristics of people prescribed different drugs which are well understood and measureable.[23] This combination of circumstances means that observational data lend themselves to a natural experiment: making direct comparisons of medication effects on important diabetes outcomes in a routine care population at the first stage of treatment intensification when SGLT2 inhibitors are commonly used.

Incentivised by the Quality Outcomes Framework, people with type 2 diabetes are regularly monitored in UK primary care, and measures of diabetic control, cardiovascular risk and renal function are recorded well in routine data.[24] We conducted a propensity-score matched, new-user cohort study to determine the effects of the three most commonly used drugs for intensification of glycaemic control after metformin monotherapy, SGLT2 inhibitors, DPP-4 inhibitors and SUs, on measures of cardiovascular and renal risk.[22]

2 | MATERIALS AND METHODS

2.1 | Data sources

We used data from the Clinical Practice Research Datalink (CPRD), which covers ~7% of the UK population and is representative in terms of age, sex and ethnicity.[25] The data contain information collected by general practitioners and primary care practitioners for routine patient care in primary care settings. Data collected include demographic information, medical diagnoses, prescriptions, laboratory test results and diagnoses made in secondary care. Our data were linked to patient-level quintiles of index of multiple deprivation (IMD) scores collated in 2015 as a measure of socioeconomic deprivation, provided by the Office of National Statistics.[26]

2.2 | Study population

To reflect prescribing of drugs used to intensify treatment of type 2 diabetes in contemporary routine clinical practice, we selected a new-user cohort of adults adding additional treatment to metformin monotherapy (study population). We first identified a study population of individuals aged ≥18 years with a new record of metformin use before any other antidiabetic medication between January 2000 and July 2017. We restricted the study to people with a minimum of 12 months of prior registration in the CPRD to allow complete data entry and to ensure they were new-users of antidiabetic drugs. From this group, we identified people prescribed one of the potential antidiabetic drug choices recommended by the National Institute of Health and Care Excellence (NICE) at the first stage of treatment intensification, defined as the "index" drug, between January 2014 and July 2017. Based on previous work we excluded people intensifying treatment with a thiazolidinedione, insulin or a GLP-1 receptor agonist as these treatments have been infrequently used in recent years and/or fall outside the standard first-stage guidance.[22] We excluded women who were pregnant before and after treatment change as guidelines are different for pregnant or breastfeeding women.

To limit the study population to people who intensified rather than changed treatment, we required that 1) a second prescription for the index drug was recorded within 60 days after the end of the first prescription and 2) the individual received a further metformin prescription between the first and second prescription for an intensification drug. We used the date of the first prescription for the first-stage intensification drug as baseline/study entry.

2.3 | Outcomes

We chose four clinical measures that are associated with future risk of cardiovascular disease or diabetic complications: glycated haemoglobin (HbA1c); systolic blood pressure (BP); body mass index (BMI); and estimated glomerular filtration rate (eGFR).[27,28] For each measure we extracted all test results for HbA1c, systolic BP, weight and height to calculate BMI, and serum creatinine to calculate eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[29] We then created four cohorts which are subsets of the study population for each clinical measure (Figure 1). To be included in a cohort, patients were required to have at least one record of the measure within 540 days prior to drug treatment intensification and at least one follow-up recording of the variable of interest. Participants in each cohort were followed until the first of: death, leaving the practice, prescription of an alternative drug treatment for type 2 diabetes, or end of study (July 1, 2017).

2.4 | Descriptive variables and covariates

Details of our cohort methodology have been published previously.[23] Baseline covariates are those recorded prior to index drug prescription. We only included measurements within 540 days prior to baseline as older values might not reflect the values at the point of treatment intensification. This time point was chosen pragmatically based on the Quality Outcomes Framework recommendation that patients with diabetes have full clinical review annually, with additional time for delays in arranging appointments and for data entry.[30] Medical diagnoses such as cardiovascular disease and retinopathy were defined as present if they were listed in the medical record on or before the date of drug intensification. We defined use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or statins as any prescription for such a drug in the year before the start of follow-up.

2.5 | Statistical analysis

2.5.1 | Propensity-score matching

Variables considered as potential confounders, based on previous work defining factors associated with drug prescription,[23] were: age; gender; ethnicity; baseline values of HbA1c, eGFR, BMI and systolic BP; baseline diagnosis of cardiovascular disease, retinopathy or current smoking; quintile of IMD score; time taking metformin before intensification; and the year that treatment was intensified.

Propensity-score matching between the three classes of drugs was used to assemble a sample in which each patient receiving SGLT2 inhibitors was matched to up to four patients prescribed DPP-4 inhibitors and up to five patients prescribed SUs. These matching goals were chosen to reflect the relative number of users in each group.

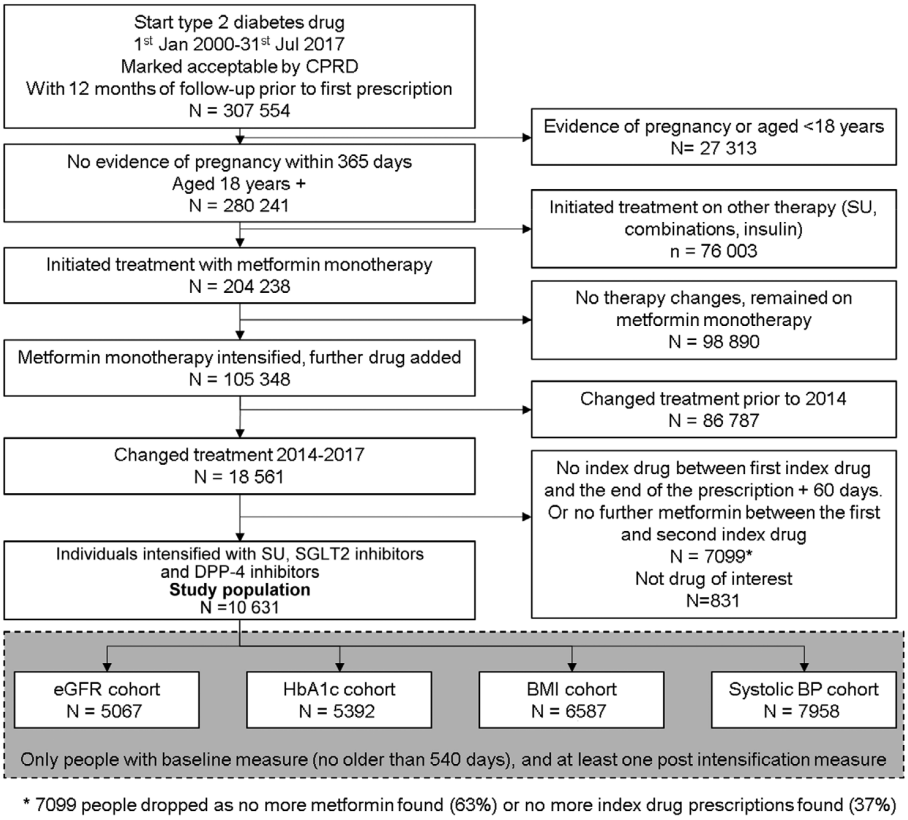

FIGURE 1 Flow diagram of study participants. BMI, body mass index; BP, blood pressure; CPRD, Clinical Practice Research Datalink; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; SU, sulphonylurea; SGLT2, sodium-glucose co-transporter-2

Each matched set had to include a minimum of one patient from each of the three treatment groups being compared. Patients were matched without replacement on the propensity score within a calliper of 0.025, ~0.2 times the standard deviation of the propensity score. The estimated propensity scores were obtained from logistic regression. An iterative approach to the selection of confounders was taken, including a potential confounder in the model if required to obtain balance of the variable across treatment groups, as measured by the standardized mean difference, accepting imbalances up to 0.2. We matched cohorts on their baseline measures of BMI, systolic BP, eGFR or HbA1c by including additional "exact" matching on each variable. To account for the variability in the number of individuals in the matched sets, patients in incomplete sets were up-weighted to give each matched set equal weight.[31] Separate propensity-score models were fitted to each sub-cohort (one for each outcome measure). Missing data in confounders were handled using a missing category approach.[32]

2.5.2 | Mixed effects linear regression

For each continuous outcome, we applied mixed effects linear regression models to the matched samples, with a random effect for patient, to estimate the mean of the measure over time, for each treatment group. We fitted a cubic model for the outcome over time. Follow-up time was split at 12, 24, 36, 60, 84 and 96 weeks, with cut-offs based on commonly reported time periods in clinical trials. Treatment effects were estimated separately in each time band. We used these models to estimate differences in means at 12 and 60 weeks compared to week zero. Overall differences across the 96-week period were obtained by averaging the period-specific treatment effect estimates and weighting by the duration of the period. To explore differential drop out over follow-up, we calculated mean baseline level of HbA1c, eGFR, systolic BP and BMI for all patients remaining in the analysis population at each follow-up time point.

2.5.3 | Sensitivity analyses

To assess the robustness of results to the assumptions made in our primary analysis we completed a series of sensitivity analyses. First, we applied the mixed effects models to 1:1:1 matched samples (rather than matched sets with varying numbers of matches). Second, we removed the censoring when patients were prescribed an additional or alternative diabetic medication, to obtain results analogous to an intention-to-treat estimate. Third, we assessed the impact of conducting a complete case analysis by imputing missing data using chained equations. Fourth, we restricted the analysis to patients who had at least one baseline and one follow-up measure for all four outcome measures, to determine whether the primary results were influenced by inclusion of patients without select measures into different cohorts. Fifth, we excluded individuals from the analysis if they had high numbers of tests for each measure (eGFR, HbA1c, BMI or systolic BP) during follow-up to assess whether frequent measurements had an impact on the findings.

2.6 | Patient and public involvement statement

Patients were not involved in the design or conduct of the study. We plan to disseminate the results through peer-reviewed publication.

2.7 | Ethics approval

The protocol for this research was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency Database Research (number 16_267). This study was also approved by the London School of Hygiene and Tropical Medicine Ethics Committee, ref: 11923.

3 | RESULTS

Within the study population of individuals who intensified from metformin monotherapy with an SU, a DPP-4 inhibitor or a SGLT2 inhibitor, 40% were women and the mean age, BMI, eGFR and systolic BP were 60 years, 33 kg/m^2, 89 mL/min/1.73m^2 and 133 mmHg, respectively (Table 1). The subcohorts for each physiological variable of interest were as follows: eGFR, n = 5067; HbA1c, n = 5392; BMI, n = 6587 and systolic BP, n = 7958. Details of the cohort selection are provided in Figure 1.

3.1 | Propensity-score matched analysis

Initial imbalances in baseline characteristics across treatment groups were minimized after propensity-score matching, for each cohort (HbA1c, eGFR, BMI and systolic BP; Figure S1). The propensity scores for SGLT2 inhibitors showed substantial overlap across the three treatment groups (Figure S2).

Table S1 describes the unmatched SGLT2 inhibitor users and Table S2 shows the number of matches identified for each cohort. The proportion of SGLT2 inhibitor users not matched ranged from 3% in the BMI cohort to 11% in the systolic BP cohort. The length of follow-up (days) and number of repeated measures did not vary substantially between each clinical variable (Table S3).

Table 2 provides the baseline characteristics of the largest propensity-score matched cohort, that for HbA1c. Baseline characteristics for the eGFR, systolic BP and BMI matched cohorts are shown in Tables S4 to S6. After propensity-score matching, cohorts were well matched on baseline covariates, and closely matched on the baseline physiological variables of interest. Figure S2 shows the percentage standardized mean difference in baseline covariates for unmatched and matched cohorts, for each measure.

TABLE 1 Description of the study population at baseline for individuals intensifying treatment from metformin monotherapy with sulphonylureas, sodium-glucose co-transporter-2 inhibitors or dipeptidyl peptidase-4 inhibitors between 2014 and 2017

	SUs N = 5010	SGLT2 inhibitors N = 1187	DPP-4 inhibitors N = 4434
Age, years	61 (13)	55 (10)	61 (12)
Women, n (%)	1988 (39.7)	474 (39.9)	1745 (39.4)
BMI, kg/m^2	32 (6)	37 (7)	33 (7)
Missing, n (%)	470 (9.4)	54 (4.5)	285 (6.4)
eGFR, mL/min/1.73m^2	89 (18)	96 (13)	88 (18)
Missing, n (%)	1683 (33.6)	493 (41.5)	1568 (35.4)
Systolic BP, mmHg	133 (14)	134 (14)	133 (14)
Missing, n (%)	837 (16.7)	293 (24.7)	880 (19.8)
HbA1c, mmol/mol	80 (21)	77 (17)	73 (16)
Missing, n (%)	2180 (43.5)	629 (53)	2085 (47)
Metformin treatment, months	40 (37)	36 (33)	44 (37)
Cardiovascular disease, n (%)	707 (14.1)	119 (10)	601 (13.6)
Heart failure, n (%)	194 (3.9)	24 (2)	146 (3.3)
Retinopathy, n (%)	868 (17.3)	181 (15.2)	861 (19.4)
ACE inhibitor/ARB treatment, n (%)	2711 (54.1)	670 (56.4)	2490 (56.2)
Statin treatment, n (%)	3530 (70.5)	819 (69)	3387 (76.4)
IMD, n (%)			
1 (least deprived)	467 (9.3)	93 (7.8)	398 (9.0)
2	485 (9.7)	99 (8.3)	378 (8.5)
3	567 (11.3)	117 (9.9)	449 (10.1)
4	643 (12.8)	99 (8.3)	427 (9.6)
5 (most deprived)	589 (11.8)	81 (6.8)	479 (10.8)
Missing	2259 (45.1)	698 (58.8)	2303 (51.9)
Smoking status, n (%)			
Non-smoker	1883 (37.6)	462 (38.9)	1642 (37.0)
Current	818 (16.3)	193 (16.3)	688 (15.5)
Ex-smoker	2297 (45.8)	532 (44.8)	2102 (47.4)
Missing	12 (0.2)	N < 5	N < 5
Ethnicity, n (%)			
White	2052 (41.5)	500 (42.1)	1944 (43.8)
South Asian	229 (4.6)	31 (2.6)	146 (3.3)
Black	122 (2.4)	9 (0.8)	61 (1.4)
Other	59 (1.2)	5 (0.4)	26 (0.6)
Mixed heritage	14 (0.3)	N < 5	16 (0.4)
Missing	2534 (50.6)	640 (53.9)	2241 (50.5)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin 2 receptor blocker; BMI, body mass index; BP, blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; IMD, index of multiple deprivation; SGLT2, sodium-glucose co-transporter-2; SU, sulphonylurea.

Note: Values for continuous values are mean (SD) and categorical values are n (%), as indicated. % values are of entire cohort. Frequencies below five not stated as per Medicines and Healthcare products Regulatory Agency database research policy.

Estimated mean values of each clinical measure for each treatment group at the analysed time points, and changes from baseline, from linear mixed models fitted within the propensity-score matched cohorts are shown in Figure 2 and Table S7.

HbA1c fell substantially after intensification from a baseline of 76 to 77 mmol/mol for all drugs, but this fall was greatest for SGLT2 inhibitor users. The mean fall at week 12 was −15.2 mmol/mol (95% CI −16.9, −13.5) for SGLT2 inhibitor users, −14.3 mmol/mol (95% CI −15.5, −13.2) for SU users and − 11.9 mmol/mol (95% CI −13.1, −10.6) for DPP-4 inhibitors users. This fall compared to baseline was similar at 60 weeks of follow-up for all drug classes. The mean difference over 96 weeks of follow-up for SGLT2 inhibitor users was

TABLE 2 Description of the propensity-score matched and weighted glycated haemoglobin cohort at baseline for individuals intensifying treatment from metformin monotherapy with sulphonylureas, sodium-glucose co-transporter-2 inhibitors or dipeptidyl peptidase-4 inhibitors between 2014 and 2017

	SUs	SGLT2 inhibitors	DPP-4 inhibitors
Number of individuals[a]	1691	481	1445
Counts after weighting	481	481	481
Age, years	56.4 (11.3)	56.3 (9.6)	56.6 (10.6)
Women, n (%)	191 (40)	191 (40)	190 (39)
BMI, kg/m^2	34.4 (5.4)	34.8 (5.5)	34.3 (5.4)
eGFR, mL/min/1.73m^2	93.5 (15.4)	93.3 (12.2)	93.3 (14.7)
Systolic BP, mmHg	133.9 (13.3)	133.7 (12.4)	133.7 (13.2)
HbA1c, mmol/mol	76.7 (18.2)	76.4 (16.8)	76.7 (16.6)
Metformin treatment, months	36.1 (34.4)	38.0 (32.9)	38.2 (35.2)
Cardiovascular disease, n (%)	57 (12)	45 (9)	51 (11)
Heart failure, n (%)	14 (3)	12 (2)	11 (2)
Retinopathy, n (%)	79 (16)	75 (16)	88 (18)
ACE inhibitor/ARB treatment, n (%)	252 (52)	278 (58)	252 (52)
Statin treatment	337 (70)	339 (70)	360 (75)
IMD			
1 (least deprived)	50 (10)	51 (11)	50 (10)
2	51 (11)	54 (11)	51 (11)
3	59 (12)	60 (12)	61 (13)
4	41 (9)	40 (8)	37 (8)
5 (most deprived)	35 (7)	37 (8)	36 (7)
Missing	245 (51)	239 (50)	246 (51)
Smoking status, n (%)			
Non-smoker	178 (37)	199 (41)	182 (38)
Current	87 (18)	75 (16)	73 (15)
Ex-smoker	213 (44)	207 (43)	225 (47)
Missing	<5	<5	<5
Ethnicity, n (%)			
White	202 (42)	194 (40)	192 (40)
South Asian	9 (2)	11 (2)	11 (2)
Black	6 (1)	7 (1)	6 (1)
Other	<5	<5	<5
Mixed heritage	<5	<5	<5
Missing	261 (54)	267 (56)	269 (56)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin 2 receptor blocker; BMI, body mass index; BP, blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; IMD, Index of multiple deprivation; SU, sulphonylurea; SGLT2, sodium-glucose co-transporter-2.

[a]Number of individuals contributing data to the HbA1c analysis, before weighting was applied. Values for categorical values are weighted mean (SD) and categorical values are n (%), as indicated, of entire cohort. After iteration of the propensity-score model, the following covariates were included in the model: age; HbA1c; eGFR; BMI; systolic BP; patient-level IMD score; and ethnicity. The groups were further matched on decile of baseline HbA1c. Figures provided are weighted means or counts. Frequencies below five not stated as per MHRA Database Research policy.

−5.4 mmol/mol (95% CI −7.4, −3.4) compared to DPP-4 inhibitor users and −1.7 (95% CI −3.7, +0.2) compared to SU users.

Baseline systolic BP was 134 to 135 mmHg and fell for SGLT2 inhibitors users throughout follow-up, but not for DPP-4 inhibitor or SU users. The mean fall at week 12 was −2.3 mmHg (95% CI −3.8, −0.8) for SGLT2 inhibitor users, −0.8 mmHg (95% CI −1.9, +0.4) for SU users and − 0.9 mmHg (95% CI −2.1, +0.2) for DPP-4 inhibitor users. At 60 weeks, systolic BP remained lower than baseline for SGLT2 inhibitor users but not for other drug classes. The mean difference over 96 weeks of follow-up for SGLT2 inhibitor users was

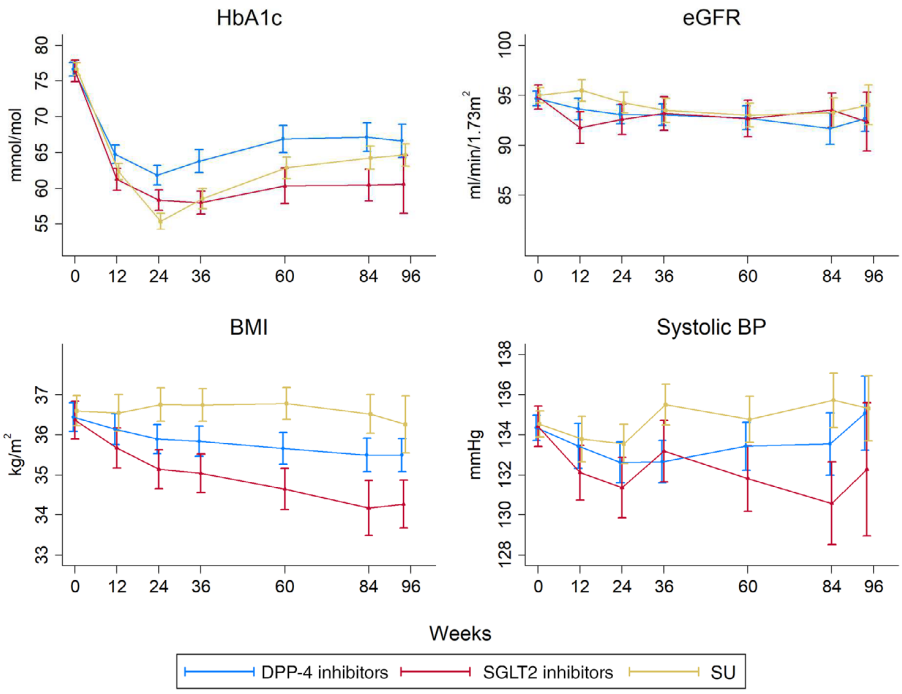

FIGURE 2 Mean (95% confidence intervals) of each clinical measure during treatment for propensity-score matched individuals after intensification with a dipeptidyl peptidase-4 (DPP-4) inhibitor, a sodium-glucose co-transporter-2 (SGLT2) inhibitor or a sulphonylurea (SU) following metformin monotherapy. BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin

−1.82 mmHg (95% CI −3.18, −0.45) compared to DPP-4 inhibitor users and −3.06 mmHg (95% CI −4.43, −1.68) compared to SU users.

Mean BMI at baseline was 36 to 37 kg/m^2 and fell compared to baseline over follow-up for SGLT2 inhibitor and DPP-4 inhibitor users. The mean fall at week 12 was −0.7 kg/m^2 (95% CI −0.9, −0.5) for SGLT2 inhibitor users, 0.0 kg/m^2 (95% CI −0.3, +0.2) for SU users and −0.3 kg/m^2 (95% CI −0.5, −0.1) for DPP-4 inhibitor users. At 60 weeks, BMI remained lower than baseline for SGLT2 inhibitor and DPP-4 inhibitor users but not SU users. These falls in BMI are equivalent to a weight loss of 2.3 kg for a DPP-4 inhibitor user and 5.0 kg for an SGLT2 inhibitor user at 60 weeks of treatment for a person 1.7 m tall, the mean height of the cohort of patients who were prescribed SGLT2 inhibitors. The mean difference over 96 weeks of follow-up for SGLT2 inhibitor users was −0.92 kg/m^2 (95% CI −1.17, −0.66) compared to DPP-4 inhibitor users and −1.67 kg/m^2 (95% CI −1.95, −1.38) compared to SU users.

Baseline eGFR was 95 mL/min/1.73m^2 and fell at 12 weeks for SGLT2 inhibitor and DPP-4 inhibitor users. The mean fall at week 12 was −3.1 mL/min/1.73m^2 (95% CI −4.1, −2.0) for SGLT2 inhibitor users, the mean increase was +0.5 mL/min/1.73m^2 (95% CI −0.4, +1.3) for SU users and the mean fall was −1.0 mL/min/1.73m^2 (95% CI −1.9, −0.2) for DPP-4 inhibitor users. At 60 weeks, the fall in eGFR from baseline was ~2 mL/min/1.73m^2 for each drug class. The mean difference over 96 weeks of follow-up for SGLT2 inhibitor users was −0.03 mL/min/1.73m^2 (95% CI −1.01, 0.94) versus DPP-4 inhibitor users and −0.78 mL/min/1.73m^2 (95% CI −1.82, −0.27) versus SU users.

During and at the end of follow-up participants who remained in the cohort were similar in their baseline characteristics to the entire cohort at baseline, suggesting that differential loss to follow-up of patients whose health status varied importantly from the entire cohort had not occurred (Tables S8–S11).

Results of all sensitivity analyses were all similar to those of the main analysis (Figures S3–S7 and Table S12). The distribution of baseline covariates for individuals excluded because of missing baseline or follow-up data was similar to that in the study population (Tables S14–S17).

4 | DISCUSSION

In the present study, we robustly estimated and compared the effects of the three drug options commonly used to intensify metformin monotherapy – SUs, SGLT2 inhibitors and DPP-4 inhibitors – on HbA1c, BMI, systolic BP and eGFR in UK primary care. In cohorts of people with similar baseline characteristics and levels of each clinical measure we show that all three drug options were associated with large falls in HbA1c, with better overall glycaemic control for people prescribed SGLT2 inhibitors. People prescribed DPP-4 inhibitors and SGLT2 inhibitors experienced falls in BMI that were sustained over the study duration, with those prescribed SGLT2 inhibitors experiencing about twice the weight loss observed for DPP-4 inhibitor users. Systolic BP fell compared to baseline at 12 weeks for SGLT2 inhibitor users but not for users of the other drug classes. Over the study duration, systolic BP was ~3 mmHg lower for those prescribed SGLT2 inhibitors compared to those prescribed SUs; however, the CIs for the estimates of systolic BP were large, and overlapped for the SGLT2 inhibitor and DPP-4 inhibitor cohorts. Users of SGLT2 inhibitors demonstrated falls in eGFR at 12 weeks of treatment but, over time, the fall in eGFR was small and similar for each drug class.

The major strength of the present study is that it reflects recent clinical practice, where relative equipoise about choice of drug class and wide national variation in choice create an opportunity for direct comparison of drug effects. Selecting patients whose drug therapy is being intensified at the same stage of treatment reduces time-related bias. We have previously examined the differences in characteristics of patients prescribed each drug class in detail and, based on this, have used propensity-score matching to achieve cohorts of patients very similar in baseline characteristics. Regular monitoring of people with type 2 diabetes in UK primary care provided extensive data, enabling us to use the vast majority of participants from our baseline cohort for modelling each clinical variable.

The relatively short period over which SGLT2 inhibitors have been used in UK primary care, however, means that the sample size was smaller than that of many primary care database studies, with a follow-up of 2 years, shorter than recent clinical trials. This means that we can only examine class effects and the study would be underpowered to detect drug-specific effects and endpoints such as cardiovascular disease mortality. We classified the start date of treatment for each intensification drug from the first record in primary care. For a proportion of patients who initiated the drugs in secondary care, this date would be misclassified. Our "baseline" values of physiological variables may therefore have been measured after treatment had started. However, this would have led to underestimation of early differences and, given the short duration of prescriptions issued in secondary care, we would anticipate that this would affect only a very small proportion of our results. Proteinuria data were insufficiently complete to use as a variable in our analysis.

Our study design focused on providing matches of patients prescribed DPP-4 inhibitors and SUs to patients prescribed SGLT2 inhibitors. This means that the results are generalizable only to contemporary SGLT2 inhibitor users in primary care who had, for example, a high BMI and well preserved renal function compared to users of other drug classes. Patients with a relative contraindication for a drug, for example, those with poor renal function (and therefore prescribed DPP-4 inhibitors or SUs), would not have been matched. Nonetheless, this study design does provide a robust comparison of the drug effects in routine care for patients for whom there was the possibility of being prescribed one of the three drug classes.

Finally, we sought to study the biological effects of the drug classes, therefore, we censored follow-up when patients commenced treatment with an alternative drug class, analogous to an "as-treated" analysis in a clinical trial. If a greater proportion of patients stopped treatment with one of the drug classes this would limit the validity of between-drug comparisons, particularly if the decision to stop treatment was associated with an outcome variable (such as failure for glycaemic control to improve). However, we saw similar results in our simulated "intention-to-treat" analysis, where we did not censor patients when they changed treatment, suggesting that this has not substantially impacted our results. As a small proportion of the cohort (4%) stop the initial drug and do not restart a different diabetic treatment (which would lead to censoring), clinical measures early on in the study period are likely to most closely represent the "as-treated" drug effects.

As we have shown previously, SGLT2 inhibitors are prescribed to a different population in UK primary care compared to patients enrolled in recent major outcome trials (Table S13).[23] Participants in our study were younger, with better renal function, and included a lower proportion of people with cardiovascular disease, heart failure and retinopathy. Our study population had poorer glycaemic control and was heavier at baseline compared to participants in recent cardiovascular outcome studies. Perhaps related to this, our study participants also showed greater improvement after initiating SGLT2 inhibitors compared to trial participants. We found a fall in HbA1c equivalent to 1.4% after 12 weeks of treatment, while clinical trial HbA1c fall estimates range from −0.25% (95% CI −0.31, −0.20) in CREDENCE to −0.58% (95% CI 0.61, −0.56) in CANVAS.

For patients commencing SGLT2 inhibitors, the present study estimated falls in BMI compared to baseline equivalent to weight loss of 2 kg at 12 weeks for an individual 1.7 m tall. Outcome studies show weight loss ranging from 1 kg at 12 weeks in CREDENCE to 2 kg at 6 months in DECLARE-TIMI. At the end of the present study, mean weight loss compared to baseline was 5 kg for SGLT2 inhibitor users compared to 2 kg in CREDENCE and 4 kg in DECLARE-TIMI.

Falls in BP and eGFR on initiating treatment with SGLT2 inhibitors are widely recognized and, in the present study, we found striking similarities between the effects seen in clinical trials and in our routine care population, although there is substantial uncertainty around our estimates. We found a mean fall in systolic BP of 2.3 mmHg (95% CI −3.8, −0.8) compared to baseline at 12 weeks for SGLT2 inhibitor users, but no fall for those prescribed other drug classes. Trial falls in systolic BP compared to baseline range from 2.8 mmHg at 12 weeks in the CREDENCE study to 5.5 mmHg in EMPA-REG (10-mg dose arm). Over the duration of the study, our results showed a mean difference in systolic BP of −3.06 mmHg (95% CI −4.43, −1.68) compared to SU-treated patients. Estimates compared to placebo in clinical trials were very similar, ranging from −2.7 mmHg (95% CI −3.0, −2.4) in the DECLARE-TIMI study to −3.93 mmHg (95% CI −4.30, −3.56) in CANVAS.

For renal function we found a fall in eGFR of −3.1 mL/min/1.73 m^2 (95% CI −4.1, −2.0) at 12 weeks, similar to that observed at 3 weeks (−3.72 ± 0.25 mL/min/1.73 m^2) in CREDENCE and the same as that observed in CANVAS at 12 weeks (−3.1 ± 0.1 mL/min/1.73 m^2). At 60 weeks we saw a fall of −2.2 mL/min/1.73 m^2 (95% CI −3.6, −0.7), again, very similar to estimates reported in clinical trials, for example, a slope of 2.74 mL/min/1.73 m^2 per year (95% CI 2.37, 3.11) in CREDENCE. However, unlike the clinical trials, falls in eGFR in our comparison group were not different from those in SGLT2 inhibitor-treated patients, ~2 mL/min/1.73 m^2 at 60 weeks for patients treated with SUs and DPP-4 inhibitors. By contrast placebo-treated patients in CREDENCE had a slope of decline of renal function of −4.59 mL/min/1.73 m^2 per year, while in CANVAS they had a difference from baseline of −3.9 ± 0.2 mL/min/1.73 m^2 at a mean follow-up of 188 weeks.

These results demonstrate the huge value of primary care data for conducting observational research. Estimates for both improvement in glycaemic control and HbA1c were very similar to those found in previous research on intensification of treatment for type 2 diabetes using the CPRD,[19] which provides validation of our methods. This is the first study to examine how changes in BP and renal function relate to changes observed in clinical trials using CPRD data. Given the consistency of the results, we are reassured that the benefits of SGLT2 inhibitors seen in clinical trials will be maintained in routine care, although given the lower risk profile of SGLT2 inhibitor-treated patients, evidence of hard outcome benefits may take longer to accrue. This is particularly the case for outcomes related to renal function, where our results suggest that the rate of renal decline is slower in non-SGLT2-inhibitor-treated patients than that observed in clinical trials, which may reflect the overall lower risk profile (younger with higher baseline eGFR) or the tighter glycaemic control seen in patients treated with other active agents in routine care.

In conclusion, routine primary care data can be used to study the effect of the new classes of treatments for type 2 diabetes on a range of biological variables, and provide estimates that are directly comparable to those seen in controlled clinical trials. Although SGLT2 inhibitor use was associated with the largest reductions in glycaemic control, weight and blood pressure, SUs and DPP-4 inhibitors were also associated with beneficial changes, reinforcing the need for active comparator outcome trials of these drugs.

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CONFLICTS OF INTEREST

H.S.-F. is an employee of and holds shares in GSK. I.J.D. is funded by, holds stock in and has consulted for GSK. D.F. has consulted for clinical trial adjudication associated with oral hypoglycaemia medications (ACI clinical), and consulted for Boehinger-Ingelheim. A.P. reports personal fees from NovoNordisk, Boehringer Ingleheim and Lilly, outside of the submitted work. L.S. has received grants from GSK and from the Wellcome trust, the MRC, the National Institute for Health Research, the British Heart Foundation and Diabetes UK, outside of the submitted work, and is a Trustee of the British Heart Foundation. L.A.T. and E.W. have no relevant conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

S.W., L.A.T., I.D., H.S.-F., E.W. and L.S. conceived and devised the study. E.W. and S.W. analysed the data. All authors contributed to the interpretation of the data. S.W. drafted the article and all authors reviewed and edited the manuscript, and approved the version to be published. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. L.A.T. is the guarantor for the work and accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

DATA AVAILABILITY STATEMENT

All codes used in this analysis are available on the Electronic Health Records Research Group Data Compass website: http://datacompass.lshtm.ac.uk/692/. Due to CPRD licence restrictions, no further data sharing is available.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Wilkinson S, Williamson E, Pokrajac A, et al. Comparative effects of sulphonylureas, dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter-2 inhibitors added to metformin monotherapy: a propensity-score matched cohort study in UK primary care. *Diabetes Obes Metab*. 2020;1–10. https://doi.org/10.1111/dom.13970

6.4 Plots of measures for random sample

To visualise the amount of follow-up available for each individual. I selected a 10% random sample of the individuals selected after propensity score matching. **Figures 6.1-6.4** present the values over time for BMI, systolic blood pressure, eGFR and HbA1c. These plots demonstrate the value of linear mixed models to summarise the mean changes in measures between the drugs of interest. They also show the shorter follow-up for the individuals prescribed SGLT2is, as discussed in the limitations of **Paper 4**.

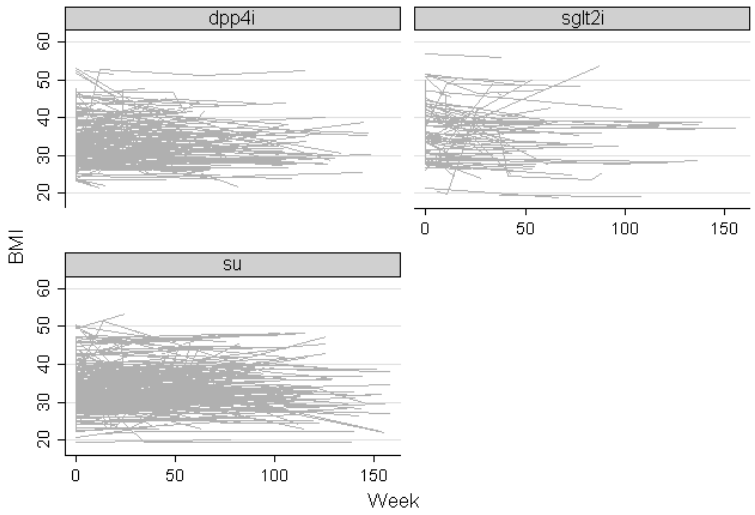

Figure 6.1 BMI during treatment, for 10% random selection of propensity score matched cohorts, following intensification with DPP4i, SGLT2i and SU after metformin monotherapy

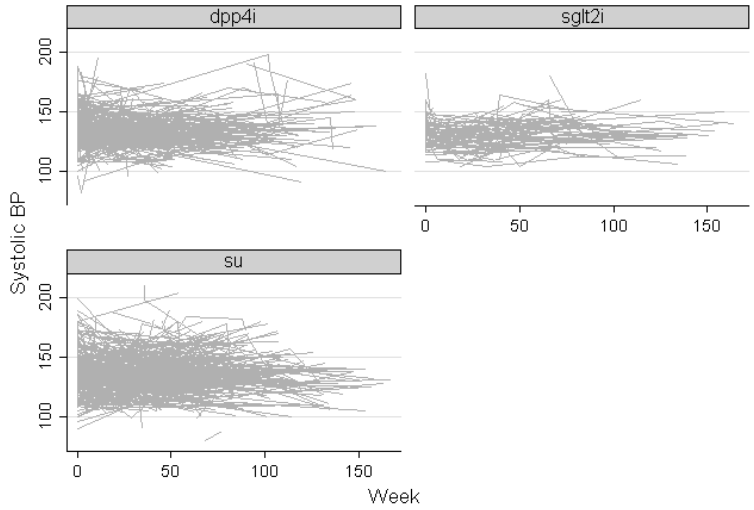

Figure 6.2 Systolic Blood Pressure during treatment, for 10% random selection of propensity score matched cohorts, following intensification with DPP4i, SGLT2i and SU after metformin monotherapy

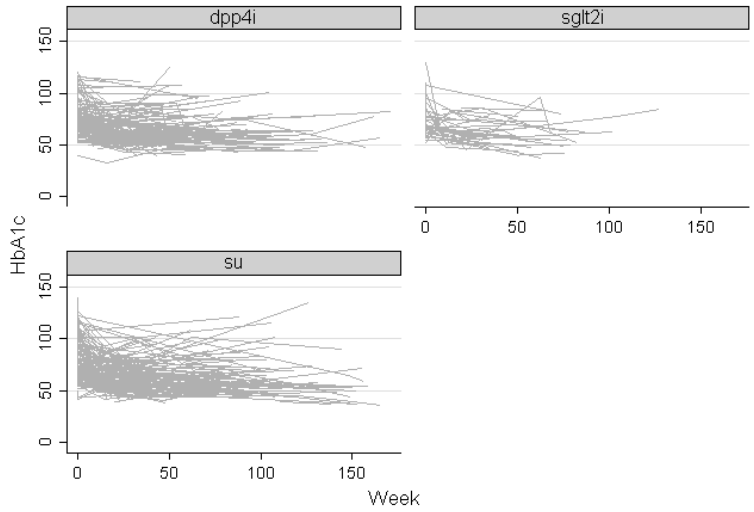

Figure 6.3 HbA1c during treatment, for 10% random selection of propensity score matched cohorts, following intensification with DPP4i, SGLT2i and SU after metformin monotherapy

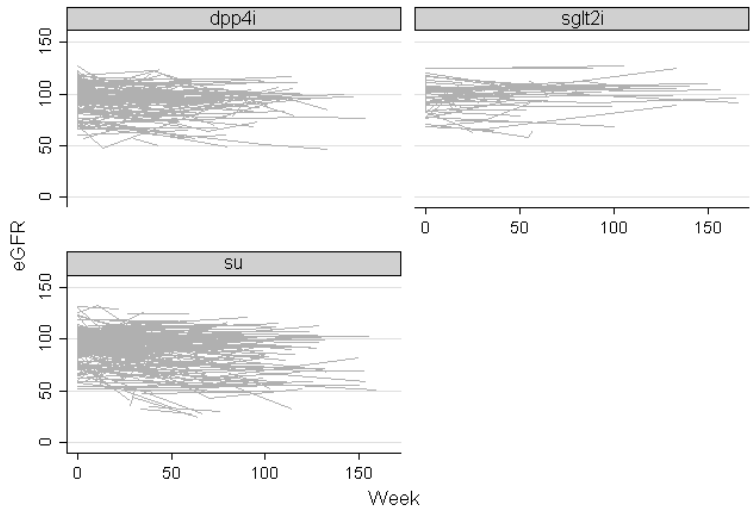

Figure 6.4 eGFR during treatment, for 10% random selection of propensity score matched cohorts, following intensification with DPP4i, SGLT2i and SU after metformin monotherapy

6.5 Investigation of clinical outcomes

As part of my PhD, I also examined clinically relevant endpoints for cardiovascular disease, kidney disease, and urinary tract infections (UTI).

Prior to completing the work, I estimated likely minimal effect sizes detectable for a renal outcome. I used estimated sample sizes for each cohort, assuming an outcome rate of 3% for renal decline with 80% power, full details in **Appendix 6**. For the smallest SGLT2i cohort, the smallest estimated difference compared to the SU group that the study could detect would be 30%.

However, this calculation was completed at the early planning stages and after development of the inclusion and exclusion criteria, the sample size was further reduced. More limited numbers in each cohort meant that the minimal effect size would need to be greater than 30%. The following section provides a summary of an exploratory analysis including crude event rates and adjusted Cox regression analyses for a range of clinical outcomes related to type 2 diabetes.

Population: Individuals that started treatment with metformin monotherapy between 2000 and 2017, and intensified treatment between January 2014 and July 2017.

Statistical analyses: Intention-to-treat analysis. Crude event rates and Cox regression models to provide adjusted hazard ratios, using the largest cohort, the sulfonylureas as the referent drug. I applied multiple imputation to impute missing baseline covariates.

Results:

Outcome		Crude outcome rates, without MI Events, rates (95% CI)			Result of Cox regression with MI HR (95% CI)
30% fall in eGFR	SU	73,	10.02	(7.97, 12.60)	Referent
	SGLT2i	6,	5.88	(2.64, 13.09)	0.97 (0.41, 2.28)
	DPP4i	46,	8.57	(6.42, 11.45)	0.92 (0.62, 1.37)
Fall in eGFR to below 30 ml/min/1.73m^2	SU	49,	5.86	(4.43, 7.75)	Not applicable
	SGLT2i	<5			
	DPP4i	29,	4.69	(3.26, 6.75)	
New diagnosis for cardiovascular disease	SU	79,	7.34	(5.90, 9.15)	Referent
	SGLT2i	8,	4.24	(2.12, 8.47)	0.75 (0.35, 1.59)
	DPP4i	45,	5.49	(4.10, 7.34)	0.78 (0.52, 1.17)
New diagnosis for heart failure	SU	46,	3.8	(2.85, 5.08)	Referent
	SGLT2i	<5			0.17 (0.02, 1.24)
	DPP4i	38,	4.12	(3.00, 5.66)	1.05, (0.67, 1.66)
UTI diagnosis	SU	83	6.64	(5.3, 8.24)	Referent
	SGLT2i	17,	8.14	(5.06, 13.09)	1.30 (0.75, 2.25)
	DPP4i	65,	6.86	(5.38, 8.75)	1.06 (.74, 1.52)

Table 6.2 Crude outcome rates prior to multiple imputation and results of Cox regression analysis with multiple imputation for type 2 diabetes related outcomes, comparing SGLT2i and DPP4i users to SU user cohort.

*Adjusted at baseline for age, gender, HbA1c, eGFR, BMI, time taking metformin before change, smoking status at baseline and ethnicity. Multiple imputation to account for missing data **also adjusted for cardiovascular disease diagnosis excluding heart failure at baseline. MI: Multiple imputation*

Conclusions: Given the small number of SGLT2i users, this analysis cannot rule out clinically relevant differences between the drugs prescribed at the first stage of treatment intensification. Point estimates indicate possible lower rates of heart failure in the SGLT2i group, and higher rates of UTI compared to the SU cohort. A study of the long-term rates for clinical outcomes related to type 2 diabetes will require longer follow-up and a greater number of users of SGLT2i. Given the growing trend for SGLT2i prescribing at this stage of treatment these data should be available soon.

7 Chapter 7: Discussion

Chapter summary

- The research presented in this thesis investigates the changing use of antidiabetic drugs and applies methods to compare these drugs at the first stage of treatment intensification, using observational health data for clinically important outcomes.
- The outputs from this research include a systematic review of the evidence for kidney function outcomes comparing oral antidiabetic drugs (**Chapter 2**) and three observational studies. The first paper describes prescribing trends for antidiabetic therapies in the UK (**Chapter 4**), the second identifies associations between patient-level factors and the drugs chosen by GPs at the first stage of intensification (**Chapter 5**). The final study is a cohort study that compares changes in eGFR, BMI, BP and HbA1c between commonly prescribed drug options (**Chapter 6**).
- The work has demonstrated that EHRs can provide insights into drug prescribing practices and closely reflect findings from RCTs for comparative assessment of new drugs.
- In this closing chapter, I summarise the strengths and limitations of each study, and discuss possible extensions of this work.

7.1 Summary of findings

Completion of this work has relied upon the use of routinely collected electronic health records from UK primary care, specifically UK CPRD GOLD. This thesis demonstrates the benefits of using electronic health records for comparative drug research, and addresses sources of potential bias when using such data. The following sections provides a brief overview of the main findings for each study, and consideration of the implications for clinical practice. Followed by a section discussing the strengths and limitations of the approaches taken as part of this research.

7.1.1 Changing use of antidiabetic drugs in the UK: trends in prescribing 2000–2017

Previously known

NHS England publishes raw prescribing numbers for all drugs prescribed by GPs on a monthly basis, and has been doing so since 2010. The data is available in an online dataset open to interrogation by the public called Open Prescribing.(125) This data shows prescribing patterns at the national level and indicated increased prescribing rates of DPP4i and SGLT2i drug classes, across the UK. However, what this data did not provide is at what stage GPs were prescribing these new drugs. A study by Sharma et al. investigated the use of first line and first stage intensification drugs in the UK between 2000 and 2013.(19) This work provides a more specific description of the prescribing trends for different stages of treatment, but did not provide contemporaneous data, and crucially does not cover the period in which SGLT2is became available, 2013 onwards.

What the study adds

Given the striking trends apparent in the Open Prescribing data that showed large increases in the use of SGLT2is in England from 2013 onwards, the study presented in **Chapter 4** shows changes in prescribing in a cohort of individuals at both treatment initiation and first stage of therapy intensification. I showed that GP prescribing has largely followed NICE prescribing guidance with increasing concordance over time. There was a large increase in prescriptions for new drug agents at the first stage of intensification. By mid-2017, DPP4is were the most prescribed first line intensification treatment (42%, 95% CI: 38, 47), overtaking prescriptions of SUs (30%, 95% CI: 25, 35). In 2017, GPs prescribed SGLT2is in 22% (95% CI: 17, 27) of treatment intensifications.

Kidney function is a key consideration for treatment choice. The DPP4i linagliptin is the only oral drug intended for first stage treatment intensification regardless of reduced kidney function without dose adjustments.(137) By contrast, recommendations regarding the use of metformin according to kidney function have changed. We showed changing prescribing practice for individuals with low renal function. However, some people with reduced kidney function are still prescribed metformin. For these people, sulfonylureas were the most commonly used first line drug, although prescribing of DPP4is for this subgroup has increased.

In this work, we also identified distinct differences in prescribing practice across the countries of the UK. GPs in Northern Ireland prescribed SGLT2is in 18% (95% CI: 11, 24) of first stage intensifications, whereas those in England used them in 9% (95% CI: 7, 11).

7.1.2 Factors associated with choice of intensification treatment for type 2 diabetes after metformin monotherapy: a cohort study in UK primary care

Previously known

In the analysis of **Paper 2 (Study of prescribing trends),** a number of observations influenced the next stage of work.

1. GP prescribing practice changed with the availability of new drug options

2. People with reduced renal function received different drug options

3. Prescribing varied across regions of the UK

Evidence from wider literature indicated that GP prescribing can be influenced by drug marketing and that local practice guidelines such as those produced by clinical commissioning groups (CCGs) may limit availability of more expensive drug options without clear evidence of benefit. At the patient level, some drugs may be favoured, or contraindicated according to patient characteristics. During the period of this study it was thought that SGLT2is would not be effective for people with CKD.(138) SGLT2is also promote weight loss.(139)

Previously published research in other drug areas suggested that GPs might favour certain patients when first prescribing new drugs, a phenomenon known as channelling. Understanding which factors influence prescribing was important before completing an outcome study.

What the study adds

The study provides a comprehensive description of the patient characteristics associated with prescribing of SUs, DPP4i and SGLT2is between 2014 and 2017, at

the first stage of treatment intensification. The study showed evidence of expected associations between patient factors and prescribing, based on the characteristics of the drug, and others that were unexpected.

Notably, the analysis showed preferential prescribing of new drugs according to non-clinical characteristics, with younger, more wealthy and white people being more likely to receive newer drug options. This suggested inequality of prescribing. Both DPP4is and SGLT2is were favoured for individuals with better glycaemic control: in people with HbA1c greater than 75, the odds ratios for prescription of newer drugs compared to SUs was 0.70 (95% CI 0.56 to 0.88) and 0.76 (95% CI 0.52 to 1.12) for DPP4i and SGLT2is intensification respectively. Furthermore, people that were overweight or obese were more likely to received SGLT2is and DPP4is. These underlying clinical differences could also be associated with future outcomes.

This paper therefore influenced the design of the final analysis. The study demonstrated that despite people being at the same stage of treatment, there were still systematic differences in the patient populations receiving each drug.

7.1.3 Comparative effects of sulfonylureas, DPP4is and SGLT2 inhibitors added to metformin monotherapy: a propensity-score matched cohort study in UK primary care

Previously known

Evidence from clinical trials including EMPA-REG, CANVAS, DECLARE-TIMI and CREDENCE indicated that SGLT2is may benefit patients, not just by reducing blood glucose, but also by reducing long-term cardiovascular and kidney disease risk. However, these studies were limited to people with increased risk for cardiovascular disease, above the presence of type 2 diabetes.(55-57, 140) People that received SGLT2is in practice do not mirror the increased cardiovascular risk profiles of the individuals included in these trials. This means that the generalisability of the findings from RCTs to the population receiving SGLT2i in routine clinical practice is still unknown. Differences between the study populations of the RCTs and the population included in our studies are large and potentially important to disease progression and outcomes, **Figure 7.1**, and **Table 7.1**

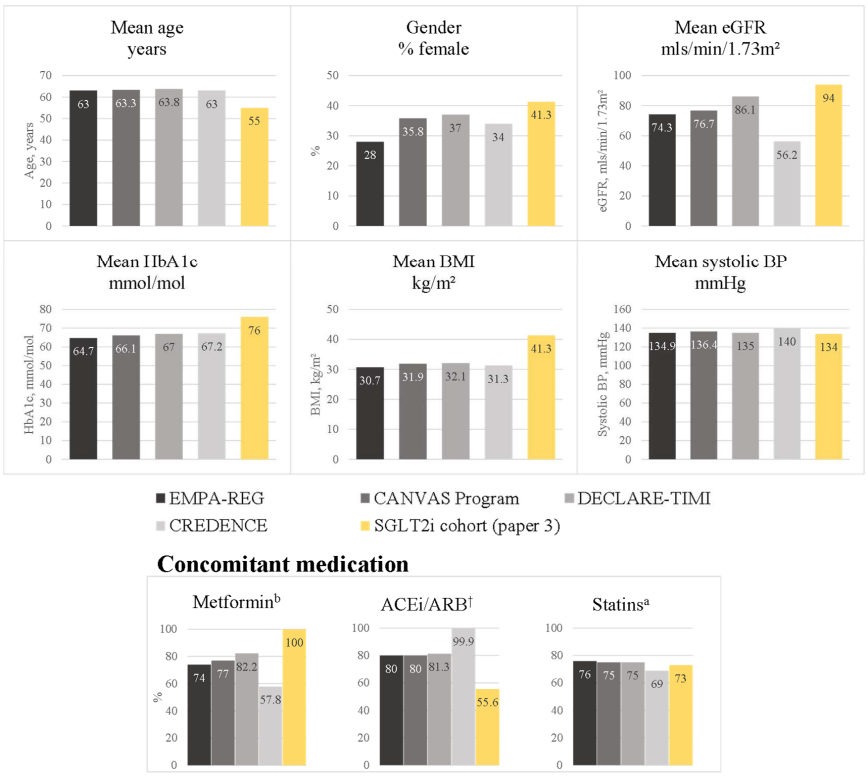

Figure 7.1 Comparison of people intensifying metformin monotherapy in the UK (Paper 3) to people included in SGLT2i RCTs.(51, 63, 126, 143) Where studies have not provided overall means or percentages, I used the placebo group statistics.

Abbreviations: SGLT2i: Sodium-glucose co-transporter-2 inhibitor, HbA1c: Haemoglobin A1c, eGFR: estimated glomerular filtration rate, BMI: Body mass index, BP: Blood pressure, ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin 2 receptor blockers. [†]Renin-angiotensin-aldosterone system inhibitors (CANVAS and CREDENCE) where ACEi/ARB statistics not available, [a]Statins or ezetimibe (DECLARE-TIMI), [b]biguanides (CREDENCE).

	EMPA-REG (2)	CANVAS (3)	DECLARE-TIMI (4)	CREDENCE (5)	Current study**
Mean age (years)	63	63	64	63	56
Female (%)	28	36	37	34	40
Mean HbA1c (mmol/mol)#	65	66	67	67	76
Mean Systolic BP (mmHg)	135	136	135	140	134
Mean BMI (kg/m^2)	31	32	32	31	34
Mean eGFR ($mls/min/1.73m^2$)	74	77	86	56	92
Cardiovascular disease (%)	98.9[c]	65.6	40.8	50.4	11
Retinopathy (%)		21		43	16
Heart failure (%)	10.1	14.4	10.0	14.8	2
Concomitant medications					
Prevalent metformin users	74	77	82	58[a]	100
ACE Inhibitor users	80	80[†]	81[$]	100[†]	54[$]
Statin users	76	75	75[b]	69	73

Table 7.1 Comparison of individuals included in our HbA1c matched analysis to individuals included in main SGLT2 inhibitor cardiovascular outcome trials.(55-57, 140)

Where studies have not provided overall means or percentage, we have provided the placebo group statistics. #converted from % if data not given, **For HbA1c matched cohort, [a] biguanides, [†]Renin-angiotensin-aldosterone system inhibitors, [$]ACE Inhibitors or Angiotensin receptor blockers, [b] Statin or ezetimibe, [c] Cardiovascular risk factors (includes coronary artery disease, history of myocardial infarction, coronary artery bypass graft, history of stroke, peripheral artery disease, coronary artery disease and cardiac failure)

Abbreviations: SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4 inhibitors, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, HbA1c: Haemoglobin A1c, eGFR: estimated glomerular filtration rate, BMI: Body mass index, BP: Blood pressure, ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin 2 receptor blockers.

According to the findings from **Paper 3**, and summarised in **Table 7.1** and **Figure 7.1**, people that initiated SGLT2is in routine practice after metformin monotherapy, were generally younger (by approximately 8 years) than individuals included in the RCTs, with higher BMIs and higher HbA1c. The RCTs also included lower proportions of women compared to those treated with SGLT2is in UK primary care. Background therapies were also different. In selection of our cohort, we required that all individuals were prescribed background metformin therapy, in line with recommendations of NICE. In the RCTs, background use of metformin was between 56.2% (CREDENCE) and 86.1% (DECLARE-TIMI).(56, 57)

In addition to providing evidence for different patient populations to those treated in primary care, the RCTs were also limited in that they were placebo-controlled and so did not provide insights into the comparative benefits of the commonly prescribed first stage intensification drugs.

What the study adds

This study measures the effects of the three most commonly prescribed treatments used at the first stage of intensification in routine primary care settings. The study compared the drugs in three-way comparisons, from the point of starting new first stage intensification medication. By selecting people to be at the same stage of intensification and then using propensity score matching, all individuals had similar values at baseline for important clinical factors. The results show differences between SGLT2is, SUs and DPP4is, in the changes of eGFR, systolic blood pressure, BMI and HbA1c over 96 weeks post drug-initiation. SGLT2is were associated with greater falls in HbA1c and BMI compared to SUs and DPP4is. In the SGLT2i group, HbA1c fell by 16 mmol/mol (95% CI: 14, 19) at 60 weeks,

compared to 10 mmol/mol (95% CI: 8, 12) and 14 mmol/mol (95% CI 12, 15) in the DPP4i and SU treated cohorts. Considering BMI, the SGLT2i group fell by 1.7 kg/m^2 (95% CI: 1.4, 2.1) and the DPP4i group fell by 0.8 kg/m^2 (0.6, 1.0) whereas the BMI in the SU group did not appear to change (0.2 kg/m^2, 95% CI: 0.0, 0.4). Systolic BP fell for SGLT2i users over follow-up but not for those prescribed DPP4i or SUs. Mean eGFR decreased over time for each drug class, and was similar across classes at 96 weeks.

The study presented has closely replicated the findings from clinical trials. As CRENDENCE and EMPA-REG have shown improved cardio-renal outcomes for people using SGLT2is, the results suggest that these benefits could be realised in routine settings, and in a broader patient population. Though recently updated ADA-EASD treatment guidelines now encourage prescribing of SGLT2is to people with increased cardiovascular risk.(41)This work suggests that SGLT2is should also be considered for lower risk populations. However, further studies are warranted once more data has accrued to investigate whether the improved outcomes are realised in lower risk populations.

7.2 Strengths and limitations

The research included in this thesis uses routinely collected data from UK primary care (CPRD GOLD). The following section outlines the strengths and weaknesses of using UK primary care data to complete these studies.

7.2.1 Strengths

Representative sample

CPRD GOLD is a representative sample of the UK population.(88) Most of the clinical trials of type 2 diabetes drugs and long-term outcomes are restricted to people with cardiovascular risk factors. By using data from a large sample of UK GPs, the results from these studies should be generalisable to the UK type 2 diabetes population, as treated in routine care. The work presented in this thesis therefore adds to results from clinical trials.

People with type 2 diabetes are well monitored in UK primary care

In the UK, treatment for people with type 2 is delivered predominantly in primary care, and QOF incentivisation has ensured good monitoring of this group, outlined in **Chapter 3**. There is high level of recording of the variables of interest including blood pressure, HbA1c, eGFR and BMI and this minimises information bias.(93)

Prescribing data to identify stage of treatment intensification

This thesis predominantly focusses on the drugs prescribed by GPs at the first stage of treatment intensification. I developed methods to ensure that all individuals included in the studies have first received a prescription for metformin, and then received a new drug to intensify treatment. This treatment pattern reflects the prescribing recommendations issued by NICE for the intensification of treatments for type 2 diabetes. Prescribing data is also well recorded in the CPRD GOLD dataset, as discussed in **Chapter 3**. Prescriptions issued by GPs are automatically recorded by the VISION system and so accurately reflect the drugs prescribed by GPs. The research presented, therefore, shows prescribing at a well-defined point in treatment. As prescribing data is automatically recorded in the database, the potential for misclassification of disease and treatment stage is minimised.(88, 141)

7.2.2 Limitations

Generalisability

CPRD GOLD only contains records of prescriptions from primary care. However, secondary care prescribers may be more prone to start people on newer drug options, compared to their colleagues in primary care. People intensified in secondary care settings would not be apparent in the record until the GP provides further prescriptions, and to be included would need to survive until they see their GP. I would therefore miss very sick people that do not survive long enough to receive the prescription. If diabetic specialists prefer one drug class for people who are sicker, this could result in a biased estimation of effect. However, in **Paper 3 (Patient level factors associated with prescribing)**, when evaluating baseline characteristics of the three cohorts, individuals receiving SGLT2is appeared to be healthier, younger and with higher kidney function than the SU and DPP4i cohorts. Therefore, there is no indication that the people receiving SGLT2i initiators received these drugs because they were systematically referred to secondary care settings for more specialist treatment of their diabetes.

Selection bias

Inclusion in my studies relies primarily on prescription data.

For **Paper 4 (Comparative study of drugs on continuous variables)**, eligibility relies upon both prescription data and availability of repeated measures for HbA1c, eGFR, BMI and systolic BP.

Given care recommendations and QOF incentivisation, people with diabetes receive regular reviews of their diabetes care.(112) There are various factors that might

influence the frequency with which tests were completed. These might include: i) low renal function, ii) access to blood testing facilities, iii) patient tendency for, or lack of self-care, or v) development of possible drug side-effects. Each of these factors may also be associated with outcomes. If, for example, a GP was concerned with a falling eGFR, the GP may ask a patient to attend more regularly for closer monitoring. This individual would therefore have a higher chance of entering the cohort and then contribute more data to the analysis than those for whom the GP was not as concerned. Hence, the findings from the study may be reflective of those sicker individuals receiving frequent tests.(141)

In clinical trials, differential loss to follow-up is an important factor for consideration. Similarly, in **Paper 4 (Comparative study of drugs on continuous variables)** some individuals might drop out, or be selected out of the study, by being treated in other settings, where data is not captured by CPRD. Therefore, those who become very sick would be lost from the follow-up. To assess whether this might have occurred I examined the baseline characteristics for individuals contributing data at each time point in the analysis, to assess if imbalance in the baseline measure occurred over time. For each of HbA1c, eGFR, BMI and systolic BP, balance in the baseline measures were maintained despite fewer people contributing data over time. This indicates that differential attrition was limited, though without the information of reasons for loss to follow-up further assertions are not possible.

Time-related bias

Time-related bias can be induced when time is misclassified as unexposed or exposed between treatment groups, and is particularly prevalent when comparing a treated to a non-treated group. In 2018, Suissa published a comment on the quality of

observational studies of SGLT2is. In the report, he noted two major sources of time-related bias: immortal time bias and 'time-lag' bias.(77) Immortal-time bias stems from differences in the allocation of time between entering the study and first exposure. In **Paper 3** and **Paper 4**, people were excluded if they did not survive long enough to receive additional metformin or two prescriptions of the index drugs. The sickest people could be hospitalised or die in the period between the two required drug prescriptions. However, the reasons for using this criterion was to avoid misclassification of treatment (switching rather than intensification). As detailed in **Section 1.1** and **5.4** a sensitivity analysis demonstrated negligible impacts on the effects estimates. On balance, this seems to be the most appropriate option.

Bias can be induced where comparisons are made between people at different stages of disease. This work used treatment patterns to identify people at the same stage of treatment. All individuals included in **Papers 3** and **4** had first received treatment with metformin monotherapy, followed by one of SU, SGLT2i and DPP4i. In **Paper 3 (Patient level factors associated with prescribing)** the length of time between the first metformin prescription and the time of SU, DPP4i or SGLT2i prescription was 1,182 days (SD: 1,103), 1,320 days (SD: 1,105) and 1,137 days (SD: 1,023) respectively. This indicates that the cohorts were similar in terms of disease duration and suggests that the risk of comparing different stages of disease was low.

However, this could be an imperfect proxy for disease severity. In **Paper 3 (Patient level factors associated with prescribing)**, the finding that non-clinical characteristics, such as being older or of South Asian ethnicity, were associated with less frequent prescribing of newer agents, was unexpected. The assumption made was that in using prescribing data, the population was limited only to individuals at the same stage of disease. Thus, the prescribing pattern was a proxy for disease

severity. The likelihood of being at a later stage of disease may be associated with both the prescribing choice and one of the outcomes. Though we adjusted for other proxies of disease intensity such as time from metformin initiation, and baseline HbA1c, these may not have fully accounted for disease severity perceived by the prescriber. Thus, disease severity may still be acting as a confounder of the associations. For example, GPs may have selected people of South Asian ethnicity for intensification at a later stage of disease, compared to white people. In this instance, SUs may be favoured due to their long-established evidence for HbA1c reduction. Disease severity could still be confounding associations between prescribing and patient characteristics.

Adherence

CPRD GOLD data does not include adherence to medications or whether the patient collects the prescription from the pharmacy. People with type 2 diabetes are exempt from prescribing charges, and so the cost of prescriptions should not affect adherence. Other factors may limit an individual's likelihood of collecting and taking prescribed medications and may also affect future outcomes. Traits such as health-seeking behaviour, adherence to concurrent prescribing and comorbidities, may induce bias into the estimates of effect, as outlined in **Section 3.2.** This is a potential source of bias for **Paper 4 (Comparative study of drugs on continuous variables)** as misclassification of true medication exposure may bias estimates. For example, someone exhibiting health-seeking behaviours may request newer drug options such as the SGLT2is more than the older SUs. These individuals may be more likely to exercise and achieve weight loss over time. This would induce a bias in favour of the SGLT2i cohort for BMI reduction compared to the SU cohort.

In requiring two prescriptions for the drug of interest, the cohorts are limited to people not experiencing early adverse events who stop taking the medication. The outcomes observed will be limited to only those people that were initially tolerant of treatment. This may introduce a bias, with drugs appearing to be more beneficial than in the population.(142) As comparisons are made between drugs, with the same set of inclusion criteria, differences observed between groups would be biased if one drug had a higher rate for early side effects than another.

Paper 2 (Study of prescribing trends) and **Paper 3 (Patient level factors associated with prescribing)** are focussed on the GP prescribing trends, without looking at outcomes, so will not be effected by bias induced by differential adherence to prescribing.

Time-varying exposures

For **Paper 4 (Comparative study of drugs on continuous variables)**, we censored individuals when they changed treatment. The reason for doing this is that the outcomes of interest may lead to changes in prescribing and the aim was to compare the biological effects of the drug. In the context of hard outcomes such as kidney failure, if a GP changes treatment because of changes in eGFR, an as-treated approach would miss the kidney failure outcome, but the drug may have induced it. For continuous measures of covariates, the bias induced would be less severe as we observe all changes in kidney function over time. However, even after the drug is no longer prescribed, there may be a lag in terms of effect on outcomes.(142) For this reason, an 'intention-to-treat' analysis was also included for comparison, where only the prescriptions at baseline were accounted for, and changes in treatment did not induce censoring. Some evidence of the expected overlap of drug effects are

apparent towards the end of follow-up in the intention-to-treat that is not seen in the as-treated analysis. For example, in the intention-to-treat HbA1c analysis, at 60 weeks the three drug cohorts appear to converge SU: 64.2 mmol/mol (95% CI: 62.9, 65.6 mmol/mol), SGLT2i: 61.6 mmol/mol (95% CI: 59.1, 64.1 mmol/mol) and DPP4i: 67.1 mmol/mol (95% CI: 65.5, 68.8 mmol/mol), which is not as seen in the as-treated cohort (SU: 62.9 mmol/mol (95% CI: 61.4, 64.4 mmol/mol), SGLT2i: 60.3 mmol/mol (95% CI: 57.9, 62.8 mmol/mol) and DPP4i: 66.9 mmol/mol (95% CI: 65.0, 68.8 mmol/mol)). This suggests that the as-treated analysis is more informative of the biological action of the drugs compared to the intention to treat analysis.

Confounding by indication

Confounders are variables that are both associated with the outcome and exposure, and not on the causal pathway between exposure and outcome. Confounding by indication, where a covariate is both an indication for treatment, and is associated with the outcome, was addressed in this work. A primary aim of **Paper 3 (Patient level factors associated with prescribing)** was to investigate the prescribing practice according to clinical baseline factors to establish if they differed systematically between groups. It showed that they did differ, and the clinical factors associated with prescribing are likely to be associated with future outcomes. The study found that people prescribed SGLT2is, on average, had higher eGFR at baseline. As eGFR was an outcome of interest for **Paper 4**, in the cohort study analysis I matched on baseline factors that might act as confounders. Though we achieved good balance on the measured variables, there is still potential that there were unmeasured confounders, which induced bias.

Unmeasured and residual confounding

Despite taking steps to deal with confounding in **Paper 3 (Patient level factors associated with prescribing)** and **Paper 4 (Comparative study of drugs on continuous variables)** there are still likely to be sources of unmeasured and residual confounding. Aspects of an individual that are apparent to a GP may not be recorded in the health record.

For **Paper 3 (Patient level factors associated with prescribing)** there may have been unmeasured clinical reasons for favouring SUs for people of South Asian or Black heritage. Ethnicity is associated with different pathophysiology of diabetes and treatment risks and so could explain divergence of prescribing practice from people of white ethnicity.(143)Another important example for my work is frailty. Frailty is a complex presentation that is not be completely represented by the health record, but may influence both prescribing practice and future outcomes, as in in **Paper 4**. Probability of prescribing for each drug could differ. GPs may use SUs with more caution in individuals that have increased risks associated with hypoglycaemic attacks, as SUs are associated with higher rates of hypoglycaemia.(144) For a frail individual, a hypoglycaemic attack can be potentially catastrophic, leading to falls and periods of hospitalisation.(2) Frail people are also at higher risks for adverse health outcomes.(145)

Another piece of information not considered are prescriptions for structured nutritional education or exercise programmes. At treatment intensification, GPs may increase lifestyle interventions.(40) If individuals made changes to improve their health at the same time as treatment escalation, the estimates will include the effects of these interventions. This work may therefore overestimate the effect of each of these drugs on measures such as BMI and HbA1c. If GPs favoured prescribing of

SGLT2is to people more prone to embrace lifestyle changes, then the findings that SGLT2is lead to larger reductions in BMI compared to DPP4is or SUs may be biased.

In **Paper 4 (Comparative study of drugs on continuous variables),** I used propensity scores to balance the baseline covariates in each group, as a result, all people with the same propensity score will have the same distribution of known confounders.(146) After matching on propensity scores, I showed that individuals in the matched cohorts were similar on both continuous and categorical covariates. For example, prior to matching the proportion of individuals with the most deprivation, according to IMD, in the SU group was 21%, compared to 17% in the SGLT2i cohort. After matching this was more similar between at the cohorts, 15% and 16% in the SU and SGLT2i cohorts respectively. However, the IMD only serves as a proxy for individual-level deprivation. IMD is an area-level proxy for socioeconomic status based on an individual's post-code so will not fully adjust for individual-level differences such as income, which may be associated with both prescribing practice and future outcomes, thus leading to residual confounding.(147) The effect of the bias on effect estimates could be in any direction. If high socioeconomic status were associated with SGLT2i prescribing and closer control of BMI, the effect of SGLT2is leading to reduction in BMI would be overestimated due to the residual confounding by socioeconomic status.

Missing data

Though the population of interest are a monitored group of individuals, this does not remove the potential for missing covariate data to bias effect estimates. **Paper 3 (Patient level factors associated with prescribing)** shows that kidney function was

associated with drug prescribing choice, but there was a high proportion of missing data. GPs may test kidney function more for those with a history of eGFR decline. Equally, as the SGLT2i class requires good renal function to reduce blood glucose, GPs can only prescribe SGLT2is to those people that have had recent eGFR tests and with good patterns of kidney function in recent years.

In both **Paper 3 (Patient level factors associated with prescribing)** and **Paper 4 (Comparative study of drugs on continuous variables)**, I used a range of approaches for dealing with missing data at baseline.

For both studies I used complete case analyses. For results from the complete case analysis to be unbiased for the general population the method relies upon the assumption that data is missing completely at random (MCAR), or at least missingness is not related to the outcome, given the observed predictors.(127)

In **Paper 3 (Patient level factors associated with prescribing),** I then applied multiple imputation in the primary analysis to handle missing data in covariates, and presented the results of a complete case analysis as supplementary information (**Appendix 5, Supplementary Table 3)**. The results from both analyses are very similar. Results from the complete case analysis have wider confidence intervals for the estimates, which is expected given the loss of data for those excluded.

For **Paper 4 (Comparative study of drugs on continuous variables)** the primary analysis dealt with missing baseline covariate information using a missing indicator approach. Missing values of continuous covariates were replaced by the mean for the sample, and a missing indicator was included in the propensity score model.(148) This method was selected as multiple imputation with propensity scores require the full analysis to be completed across multiple imputed datasets. In the case of this

study, we modelled the change in the outcomes over time after treatment change, and applications of propensity scores in this setting have not been commonly used. The missing indicator method was a simpler approach that enabled more data to be included in the models. I contrasted results from the primary analysis to an approach that used multiple imputation to estimate baseline covariates. The propensity score was an average propensity from multiple imputed datasets, and used this to match cohorts at baseline. The results of these two approaches are very similar, **Paper 4 Figure 2**, and **Appendix 6, Supplementary figure 5** however it is not possible to test the underlying assumptions for these methods, as I do not have the missing data. Though not applied here, other methods to account for missing not at random (MNAR) missingness patterns are available in the literature. Such sensitivity analyses could investigate how robust findings are to different missingness patterns.(149) These approaches include selection model and pattern-mixture models.(150)

Generalisability of methods

The methods applied in this context benefitted from the relative equipoise in the prescribing decision at treatment intensification. Given that guidelines had not made strong recommendations for one drug, this stage of treatment prescribing was well suited for comparisons. Now that clinical trial evidence has grown indicating the benefits of SGLT2is, this relative equipoise is likely to diminish.(41) After changes in guidelines, clinicians will likely favour SGLT2is for people with higher cardiovascular disease risk. In other disease settings, where treatments are intensified over time, assumptions regarding relative equipoise may not hold.(151) The methods

and findings have therefore been applied to a specific prescribing practice, that occurred for a short period in time.

7.3 Future directions

The results from **Paper 4 (Comparative study of drugs on continuous variables)** indicate that this primary care data and the cohort identified can mirror the changes in eGFR, BMI, blood pressure and HbA1c identified in the recent cardiovascular outcome trials. What this work has not been able to investigate is whether these changes will translate to the reductions in patient outcomes that have been reported by clinical trials for SGLT2is in recent months. Given that the cohort identified in this thesis is a healthier population than those included in the RCTs, with lower risks for renal and cardiovascular outcomes, completion of a properly powered study of diabetes related outcomes will require more data, as shown in **Section** Error! Reference source not found.. There are two clear ways to increase numbers: (i) wait for the accrual of prescriptions and outcomes in CPRD GOLD, (ii) use the CPRD Aurum dataset to augment the numbers. These options should allow for a fully powered comparative study of outcomes for SUs, SGLT2is and DPP4is in combination with metformin.

Another possible avenue for exploration would be the heterogeneity in the type 2 diabetes population. There is a growing body of evidence showing that, within the type 2 diabetes population, there are different subtypes that respond to interventions differently. Machine learning algorithms have been applied to RCT data in post hoc analyses, revealing different outcome rates according to diabetes management and overall health that were not identified in the primary RCT analysis. In these post-hoc analyses, subgroups within the RCT populations benefitted more from weight-loss

intervention than others (Look AHEAD)(152) or intensive blood glucose lowering (ACCORD-BP or SPRINT trials).(153) Other studies have shown that electronic health records can be used to identify subgroups within the type 2 diabetes populations. Using analytical techniques such as topological data analysis and machine learning algorithms, type 2 diabetes populations appear to contain three or four subtypes with different comorbidity risk profiles. Some subtypes had higher rates of diabetic kidney disease, and others showed lower rates of comorbidities (3, 154-156) Better understanding of these subtypes could help to personalise treatments and improve patient outcomes. Repeating comparative effectiveness work, using disease subtypes as subgroups could highlight people that respond better to each of the drugs and help guide clinicians.

Such work could benefit from additional clinical information, such as genetic data from the UK Biobank. However, classification of type 2 diabetes subtypes using the data currently collected in primary care settings, without the need for additional data would allow for bigger studies and have faster impact on clinical practice.

7.4 Conclusion

With the rapid uptake of new drugs to treat type 2 diabetes in primary care practice in the UK, this thesis has demonstrated the ability for electronic health records to assess how GPs prescribe these drugs and how they compare with each other in terms of clinical variables. The studies presented indicate that prescribing practice in the UK has changed quickly over time. GPs prescribing new drugs may be influenced by both clinical and non-clinical factors. By following individuals that received these drugs in routine practice, I have been able to show similar changes in clinical variables to those reported in clinical trials. Finally, the SGLT2i cohort appear to experience greater falls in BMI and HbA1c over follow-up compared to both DPP4i and SU cohorts. This work therefore further demonstrates the potential for observational health data, with careful study design, to enrich the findings from clinical trials in real-time and in routine clinical settings.

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9 Appendix

9.1 Appendix 2: Supplementary material for Paper 1

This section provides the supplementary material for the systematic review article in chapter 2.First the PRISMA checklist ; then table S2.1 and table S2.2 detail the searches used to identify studies from Medline and Web of Science; followed by further comparisons presented in an included study that were not included in the systematic review article (table S2.3); table S2.4 contains detailed definitions of composite renal outcomes reported by the observational studies included in the systematic review; and table S2.5 and S2.6 contain checklists for used to assess study quality.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported in section, paragraph (p)
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Intro, p2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Intro, p2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods, p1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods p2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, p2, fig1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Sup tables 1 and 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, p3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, p6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, p6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods, p6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods, p5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Table S2.1: First Ovid Medline search

1	(kidney or renal or Albumin or ACR or albuminuria or CKD or creatinine or dialysis or eGFR or esrd or glomerular or GFR* or cystatinC or haematuria or microvascular or protein:creatinine or proteinurea or proteinuria).af.	1152518	Advanced
2	Renal Insufficiency/ or Cystatin C/ or Kidney/ or Kidney Diseases/ or Glomerular Filtration Rate/ or Creatinine/ or Diabetic Nephropathies/ or Proteinuria/	389625	Advanced
3	1 or 2	1161071	Advanced
4	(antidiabetic or Acarbose or Acetohexamide or Actos or Actraphane or Alogliptin or glucosidase or Amaryl or Aspart or Avandia or Avandamet or insulin or Biguanide* or Bolamyn or Bydureon or Byetta or Calabren or Canagliflozin or Chloropropamide or Competact or Dacadis or Daonil or Dapagliflozin or Degludec or Determir or Diabetamide or Diabinese or Diagemet or Diaglyk or Diamicron or Dimelor or Dipeptidyl or DPP-4 or DPP-4i or Duclazide or Duformin or Edicil or Empagliflozin or Enyglid or Eucreas or Euglucon or Exenatide or Forxiga or Galvus or Glargine or Glibenclamide or Glibenese or Glibornuride or Gliclazide or Gliflozin or Glimepiride or Glinides or Glipizide or Gliquidone or Glitpins or GLP-1 or Glucagon-like or Glucamet or Glucient or Glucobay or Glucophage or Glutril or Glyconon or Glymese or Glymidine or Guar or Guarem or Guarina or Glurenorm or Humaject or Humalog or Humulin or Hypurin or Hypurin or incretin or Innolet or Insulatard or Insulin or Invokana or aspart or degludec or detemir or glargine or Isophane or Lispro or Insuman or Invokana or Isophane or Janumet or Januvia or Jentadueto or Komboglyze or Laaglyda or Lantus or Levemir or Libanil or Linagliptin or Liraglutide or Lisophane or Lispro or Lixisenatide or Lyxumia or Malix or Meglinitides or Metabet or Metformin or Minodiab or Dapagliflozin or Pioglitazone or Saxagliptin or Vildagliptin or Metsol or Mixtard or Nateglinide or Nateglinide or Nazdol or Neuphane or Niddaryl or Novomix or NovoNorm or Onglyza or Orabet or Penmix or Pioglitazone or Prandin or Protamine or Pur-in or Rastinon or Repaglinide or Romozin or Rosiglitazone or Maleate or Saxagliptin or Semi-Daonil or Sitagliptin or Starlix or SU or Sukkarto or Sulfonylurea or Sulphonylurea or Tempulin or Tolanase or Tolazamide or Tolbutamide or Trajenta or Tresiba or Troglitazone or TZD or thiazolidinedione or Victoza or Vildagliptin or Vildagliptin or Vipdomet or Vipidia or Xigduo or Zicron).ab,ti.	332666	Advanced
5	Hypoglycemic Agents/	48689	Advanced
6	4 or 5	346663	Advanced
7	(Case-control* or Cohort* or Comparative effectiveness* or Cross-sectional or Meta-analysis or Nonexperimental or Pharmacoepid* or Prospectiv* or RCT* or Trial*).ab,ti.	1487119	Advanced
8	Clinical Trial/ or Comparative Effectiveness Research/ or Cohort Studies/ or Cross-Sectional Studies/ or Case-Control Studies/	1063484	Advanced
9	7 or 8	2064294	Advanced
10	3 and 6 and 9	6491	Advanced
11	limit 10 to (male and female and humans and yr="1980 -Current")	4083	Advanced

Table S2.2 First search Web of science

Set	Results	Criteria
# 4	532	#3 AND #2 AND #1 *Timespan=1980-2016* *Search language=Auto*
# 3	Approx. 559,338	TI=(antidiabetic or Acarbose or Acetohexamide or Actos or Actraphane or Alogliptin or glucosidase or Amaryl or Aspart or Avandia or Avandamet or insulin or Biguanide* or Bolamyn or Bydureon or Byetta or Calabren or Canagliflozin or Chloropropamide or Competact or Dacadis or Daonil or Dapagliflozin or Degludec or Determir or Diabetamide or Diabinese or Diagemet or Diaglyk or Diamicron or Dimelor or Dipeptidyl or "DPP-4" or "DPP-4i" or Duclazide or Duformin or Edicil or Empagliflozin or Enyglid or Eucreas or Euglucon or Exenatide or Forxiga or Galvus or Glargine or Glibenclamide or Glibenese or Glibornuride or Gliclazide or Gliflozin or Glimepiride or Glinides or Glipizide or Gliquidone or Glitpins or "GLP-1" or Glucagon-like or Glucamet or Glucient or Glucobay or Glucophage or Glutril or Glyconon or Glymese or Glymidine or Guar or Guarem or Guarina or Glurenorm or Humaject or Humalog or Humulin or Hypurin or Hypurin or incretin or Innolet or Insulatard or Insulin or Invokana or aspart or degludec or detemir or glargine or Isophane or Lispro or Insuman or Invokana or Isophane or Janumet or Januvia or Jentadueto or Komboglyze or Laaglyda or Lantus or Levemir or Libanil or Linagliptin or Liraglutide or Lisophane or Lispro or Lixisenatide or Lyxumia or Malix or Meglinitides or Metabet or Metformin or Minodiab or Dapagliflozin or Pioglitazone or Saxagliptin or Vildagliptin or Metsol or Mixtard or Nateglinide or Nateglinide or Nazdol or Neuphane or Niddaryl or Novomix or NovoNorm or Onglyza or Orabet or Penmix or Pioglitazone or Prandin or Protamine or Pur or Rastinon or Repaglinide or Romozin or Rosiglitazone or Maleate or Saxagliptin or Daonil or Sitagliptin or Starlix or SU or Sukkarto or Sulfonylurea or Sulphonylurea or Tempulin or Tolanase or Tolazamide or Tolbutamide or Trajenta or Tresiba or Troglitazone or TZD or thiazolidinedione or Victoza or Vildagliptin or Vildagliptin or Vipdomet or Vipidia or Xigduo or Zicron or Hypoglycaemic or Hypoglycemic) *Timespan=1980-2016* *Search language=Auto*
# 2	Approx. 1,428,406	TI=(Cohort* or Comparative or Nonexperimental or Pharmacoepid* or Prospectiv* or RCT* or Trial*) *Timespan=1980-2016* *Search language=Auto*
# 1	Approx. 2,999,026	TS=(kidney or renal or Albumin or ACR or albuminuria or CKD or creatinine or dialysis or eGFR or esrd or glomerular or GFR* or cystatinC or haematuria or microvascular or proteinurea) *Timespan=1980-2016* *Search language=Auto*

Table S2.1 First search Web of science, across Web of ScienceTM Core Collection, BIOSIS Citation Index, KCI-Korean Journal Database, MEDLINE, SciELO Citation Index

Table S2.3 Report of further comparisons from Hippisley-Cox and Coupland (2016) paper

Author (Year)	Kidney outcomes	Kidney outcomes recorded HR (95% CI)
Hippisley-Cox and Coupland (2016) (157)	**1** Incident severe kidney failure (Read code defined as kidney dialysis, transplantation, or CKD stage 5 based on serum creatinine values	Incident kidney failure MTF referent TZD: 2.55 (1.13, 5.74) DPP4I: 3.52 (2.04, 6.07) SU: 2.63 (2.25, 3.06) MTF+TZD: 0.71 (0.33, 1.50) MTF+SU: 0.76 (0.62, 0.92) MTF+DPP4I: 0.59 (0.28, 1.25) SU+TZD: 2.14 (1.27, 3.61) SU+DPP4I: 3.21 (2.08, 4.93) SU+TZD+MTF: 1.21 (0.75, 1.96) SU+DPP4I+MTF: 0.68 (0.39, 1.20)
Abbreviations: MTF: metformin, SU: sulfonylurea, TZD: thiazolidinedione, DPP4I: Dipeptidyl peptidase-4, CKD: Chronic Kidney Disease		

Table S2.2 Report of further comparisons from Hippisley-Cox and Coupland (2016) paper

Table S2.4 Detailed definitions of composite renal outcomes for observational studies

Author (Year)	Definition of Renal outcomes
Hung et al (2012) (158)	1: eGFR event >=25% decline, confirmed 3-12 months following 2: ESRD Defined as eGFR<15 (confirmed in 3-12 months following), ICD-9 codes for dialysis (confirmed in 3-12 months following), renal transplant 3: Mortality
Pendergrass et al (2012) (159)	1st ARF (ICD-9 code 584*)
Currie et al. (2013) (160)	Renal failure (Read code defined, covering disease areas: CKD, dialysis, transplantation, renal failure, nephritis, nephropathy, necrosis)
Hung et al (2013) (161)	1: eGFR event >=25% decline, confirmed 3-12 months following 2: ESRD Defined as eGFR<15 (confirmed in 3-12 months following), ICD-9 codes for dialysis (confirmed in 3-12 months following), renal transplant 3: Mortality
Masica et al. (2013) (162)	1: New proteinuria (based on 24-hour albumin/protein, spot protein, spot ACR, or dipstick) 2: New eGFR to <60
Hippisley-Cox and Coupland (2016) (157)	1: Incident severe kidney failure (Read code defined as kidney dialysis, transplantation, or CKD stage 5 based on serum creatinine values)
Kolaczynski et al (2016) (163)	Incident nephropathy (ICD-10 codes: E11.2 or E14.2)
Goldshtein et al. (2016) (164)	Improvements in urinary ACR (at least 20% improvement in ACR and change in KDIGO category)
Abbreviations: ESRD: End stage renal disease, ARF: Acute Renal Failure, ACR: Albumin: Creatinine Ratio, CKD: Chronic Kidney Disease, KDIGO: Kidney Disease: Improving Global Outcomes, ICD: International Classification of Diseases	

Table S2.3 Detailed definitions of composite renal outcomes for observational studies

Table S2.5 GRACE 2014 items for observational studies

	Authors, year **Scoring as Fit for Purpose: Sufficient (+), Insufficient (-)**							
Component Item	**Hung 2013**	**Hung 2012**	**Currie et al. 2013**	**Masica et al. 2013**	**Kolaczynski et al. 2016**	**Hippisley-Cox & Coupland, 2016**	**Goldshtein et al. 2016**	**Carlson et al 2016**
Data								
D1. Were treatment and/or important details of treatment exposure adequately recorded for the study purpose in the data source(s)?	+	+	+	-	-	+	+	+
D2. Were the primary outcomes adequately recorded for the study purpose (e.g., available in sufficient detail through data sources)?	+	+	+	+	+	+	+	+
D3. Was the primary clinical outcome(s) measured objectively rather than subject to clinical judgment (e.g., opinion about whether the patient's condition has improved)?	+	+	+	+	+	+	+	+
D4. Were primary outcomes validated, adjudicated, or otherwise known to be valid in a similar population?	+	+	+	+	-	+	+	+
D5. Was the primary outcome(s) measured or identified in an equivalent manner between the treatment/intervention group and the comparison group?	+	+	+	+	+	+	+	+
D6. Were important covariates that may be known confounders or effect modifiers available and recorded?	+	+	+	+	-	+	+	+
Methods								
M1. Was the study (or analysis) population restricted to new initiators of treatment or those starting a new course of treatment?	?	+	-	-	-	-	+	+
M2. If 1 or more comparison groups were used, were they concurrent comparators?	+	+	+	+	+	+	+	+
M3. Were important confounding and effect-modifying variables taken into account in the design and/or analysis?	+	+	+	+	+	-	+	+
M4. Is the classification of exposed and unexposed person-time free of "immortal time bias?	+	+	+	+	+	+	+	+
M5. Were any meaningful analyses conducted to test key assumptions on which primary results are based?	+	+	some	-	-	-	+	+

Table S2.4 GRACE 2014 items for observational studies

Table S2.6 Cochrane items for quality of RCT studies

	Authors, year **Scoring as Fit for Purpose: Sufficient (+), Insufficient (-)**						
Item	**Bakris, 2003**	**Hanefeld, 2004**	**Schernthaner et al. (2004)**	**Matthews, 2005**	**Lachin, 2011**	**Heerspink et al. 2017**	**Pan et al. 2016**
Random sequence generation (selection bias)	?	?	+	?	?	+	-
Allocation concealment (selection bias)	-	?	+	?	?	+	-
Blinding of participants and researchers (performance bias)	-	+	+	+	+	+	-
Blinding of outcome assessment (detection bias)	?	+	?	+	+	+	-
Incomplete outcome data (attrition bias)	?	+	?	?	-	+	?
Selective reporting (reporting bias)	+	+	+	+	+	+	+

Table S2.5 Cochrane items for quality of RCT studies

9.2 Appendix 3: Methods

9.2.1 Creation of diabetic drug list

Based on the literature, I used the following terms to search the CPRD Codebrowser for diabetic drugs.

Initial search terms
BNF header terms: *ctos* *maryl* *olamyn* *ydureon* *yetta* *ompetact* *iamicron* *ucreas* *orxiga* *alvus* *libenclamide * *liclazide* *limepiride* *lipizide* *lucient* *lucophage* *nvokana* *anumet* *anuvia* *ardiance* *entadueto* *omboglyze* *yxumia* *etabet* *etformin* *inodiab* *ovonorm* *nglyza* *ioglitazone* *randin* *epaglinide* *tarlix* *olbutamide* *rajenta* *ictoza* *ipdomet* *okanamet* *igduo* *ultophy* *logliptin* *anagliflozin* *apagliflozin* *mpagliflozin* *xenatide * *libenclamide* *inagliptin* *iraglutide* *ixisenatide* *ateglinide* *axagliptin* *itagliptin* *ildagliptin* *iguanide* *PP-4i* *LP-1* *lucagon-like peptide-1* *eglitinides * *GLT-2* *ulfonylurea* *ulphonylurea* *hiazolinedione* *tzd* *ntidiabetic* *sulin*: *iguanide* *antidiabetic* *ulphonylurea* *hypodermic* *insulin*"
BNF codes: 0601020* 060102* *06010201* *06010202* *06010203* *06010200* *71190600*
Product names: *ctos* *maryl* *olamyn* *ydureon* *yetta* *ompetact* *iamicron* *ucreas* *orxiga* *alvus* *libenclamide * *liclazide* *limepiride* *lipizide* *lucient* *lucophage* *nvokana* *anumet* *anuvia* *ardiance* *entadueto* *omboglyze* *yxumia* *etabet* *etformin* *inodiab* *ovonorm* *nglyza* *ioglitazone* *randin* *epaglinide* *tarlix* *olbutamide* *rajenta* *ictoza* *ipdomet* *okanamet* *igduo* *ultophy* *logliptin* *anagliflozin* *apagliflozin* *mpagliflozin* *xenatide * *libenclamide* *inagliptin* *iraglutide* *ixisenatide* *ateglinide* *axagliptin* *itagliptin* *ildagliptin* *iguanide* *PP-4i* *LP-1* *lucagon-like peptide-1* *eglitinides * *GLT-2* *ulfonylurea* *ulphonylurea* *hiazolinedione* *tzd* *sulin**glinide* *gliptin* *glymidine* *bornuride* *glutide* *guar* *nsulin* *carbose* *gliptin* *gliflozin* *xenatide* *benclamide* *liclazide* *mepiride* *lipizide* *glutide* *etformin* *glitazone* *glinide*
Drug substance name: *ctos* *maryl* *olamyn* *ydureon* *yetta* *ompetact* *iamicron* *ucreas* *orxiga* *alvus* *libenclamide * *liclazide* *limepiride* *lipizide* *lucient* *lucophage* *nvokana* *anumet* *anuvia* *ardiance* *entadueto* *omboglyze* *yxumia* *etabet* *etformin* *inodiab* *ovonorm* *nglyza* *ioglitazone* *randin* *epaglinide* *tarlix* *olbutamide* *rajenta* *ictoza* *ipdomet* *okanamet* *igduo* *ultophy* *logliptin* *anagliflozin* *apagliflozin* *mpagliflozin* *xenatide * *libenclamide* *inagliptin* *iraglutide* *ixisenatide* *ateglinide* *axagliptin* *itagliptin* *ildagliptin* *iguanide* *PP-4i* *LP-1* *lucagon-like peptide-1* *eglitinides * *GLT-2* *ulfonylurea* *ulphonylurea* *hiazolinedione* *tzd* *sulin* *vandamet* *vandia* *hlorpropamid* *ompetact* *oanil* *liquidone* *lurenorm* *uar**acarbose* *acetohexa* *actos* *aloglipti* *amaryl* *avandamet* *avandia* *bolamyn* *bydureon* *byetta* *calabren* *canaglifl* *chlorprop* *competact* *dapaglifl* *diabetami* *diagemet* *diaglyk* *diamicron* *dimelor* *enyglid* *eucreas* *euglucon* *exenatide* *forxiga*

galvus *glibencla* *gliclazid* *glimepiri* *glipizide* *glucamet* *glucient* *glucophag* *glutril* *glyconon* *glymese* *guar* *guarem* *guarina* *invokana* *janumet* *januvia* *jentaduet* *komboglyz* *laaglyda* *libanil* *linaglipt* *liragluti* *lixisenat* *lyxumia* *metabet* *metformin* *metsol* *nazdol* *niddaryl* *novonorm* *onglyza* *pioglitaz* *prandin* *rastinon* *romozin* *rosiglita* *saxaglipt* *starlix* *sukkarto* *tolbutami* *trajenta* *victoza* *vildaglip* *vipdomet* *xiapex* *xultophy* *xigduo* *zemplar* *zicron* *daonil* *dacadis* *diabinese* *duclazide* *duformin* *edicil* *empaglifl* *glibenese* *glibornur* *gliquidon* *glucobay* *glurenorm* *glymidine* *malix* *minodiab* *nateglini* *orabet* *repaglini* *semi-daon* *sitaglipt* *tolanase* *tolazamid* *troglitaz* *vipidia*
Exclusion terms
Product names: *xiapex* *collagenase* *dressin* *supple* *lubricants* *hypodermic* *soft-tissue* *needle* *flextouch* *cap* *needle* *sterile* *lancet* *unilet* *zemplar* *probioguard* *guarina* *hypoguard* *lactose* *container* *guardi* *cream* *bag* *cough* *eye* *film* *sharpsguard* *spray* *folguard* **BNF header**: *enzymes* *dressin* *supple* *lubricants* *hypodermic* *soft-tissue* *needle* *lancet* *unilet* *zemplar* *probioguard* *guarina* *hypoguard* *lactose* *container* *guardi* *cream* *bag* *cough* *eye* *film* *sharpsguard* *spray* *folguard* **BNF code**: *09040251* *72214300* *71190600* *11080100*

Appendix table 6: Terms used to create type 2 diabetes drug list

9.3 Appendix 4: Supplementary material for chapter 4

This appendix provides the supplementary material for the trends in prescribing paper (Paper 2) presented in Chapter 4.

9.3.1 4.1 Drug codes to group drugs classes into drug

productname	agent	class
gliclazide 80mg tablets	gliclazide	su
sitagliptin 100mg tablets	sitagliptin	dpp4i
gliclazide 40mg tablets	gliclazide	su
linagliptin 5mg tablets	linagliptin	dpp4i
dapagliflozin 10mg tablets	dapagliflozin	sglt2i
saxagliptin 5mg tablets	saxagliptin	dpp4i
alogliptin 25mg tablets	alogliptin	dpp4i
gliclazide 30mg modified-release tabl..	gliclazide	su
sitagliptin 50mg tablets	sitagliptin	dpp4i
glimepiride 1mg tablets	glimepiride	su
empagliflozin 10mg tablets	empagliflozin	sglt2i
canagliflozin 100mg tablets	canagliflozin	sglt2i
sitagliptin 25mg tablets	sitagliptin	dpp4i
forxiga 10mg tablets (astrazeneca uk ..	dapagliflozin	sglt2i
dapagliflozin 5mg tablets	dapagliflozin	sglt2i
metformin 1g / sitagliptin 50mg tablets	sitagliptin	dpp4i
saxagliptin 2.5mg tablets	saxagliptin	dpp4i
glimepiride 2mg tablets	glimepiride	su
glipizide 5mg tablets	glipizide	su
janumet 50mg/1000mg tablets (merck sh..	sitagliptin	dpp4i
alogliptin 12.5mg tablets	alogliptin	dpp4i
linagliptin 2.5mg / metformin 1g tabl..	linagliptin	dpp4i
empagliflozin 25mg tablets	empagliflozin	sglt2i
forxiga 5mg tablets (astrazeneca uk l..	dapagliflozin	sglt2i
trajenta 5mg tablets (boehringer inge..	linagliptin	dpp4i
gliclazide 60mg modified-release tabl..	gliclazide	su
januvia 100mg tablets (merck sharp & ..	sitagliptin	dpp4i
vildagliptin 50mg tablets	vildagliptin	dpp4i
vipdomet 12.5mg/1000mg tablets (taked..	alogliptin	dpp4i
alogliptin 6.25mg tablets	alogliptin	dpp4i
glimepiride 3mg tablets	glimepiride	su
alogliptin 12.5mg / metformin 1g tabl..	alogliptin	dpp4i
invokana 100mg tablets (janssen-cilag..	canagliflozin	sglt2i
glimepiride 4mg tablets	glimepiride	su

productname	agent	class
jardiance 10mg tablets (boehringer in..	empagliflozin	sglt2i
saxagliptin 2.5mg / metformin 1g tabl..	saxagliptin	dpp4i
glibenclamide 5mg tablets	glibenclamide	su
vildagliptin 50mg / metformin 850mg t..	vildagliptin	dpp4i
linagliptin 2.5mg / metformin 850mg t..	linagliptin	dpp4i
vipidia 25mg tablets (takeda uk ltd)	alogliptin	dpp4i
canagliflozin 300mg tablets	canagliflozin	sglt2i
dapagliflozin 5mg / metformin 1g tabl..	dapagliflozin	sglt2i
dapagliflozin 5mg / metformin 850mg t..	dapagliflozin	sglt2i
vildagliptin 50mg / metformin 1g tabl..	vildagliptin	dpp4i
empagliflozin 5mg / metformin 1g tabl..	empagliflozin	sglt2i
xigduo 5mg/1000mg tablets (astrazenec..	dapagliflozin	sglt2i
diamicron 30mg mr tablets (servier la..	gliclazide	su
januvia 50mg tablets (merck sharp & d..	sitagliptin	dpp4i
komboglyze 2.5mg/1000mg tablets (astr..	saxagliptin	dpp4i
canagliflozin 50mg / metformin 850mg ..	canagliflozin	sglt2i
januvia 25mg tablets (merck sharp & d..	sitagliptin	dpp4i
saxagliptin 2.5mg / metformin 850mg t..	saxagliptin	dpp4i
empagliflozin 5mg / metformin 850mg t..	empagliflozin	sglt2i
jentadueto 2.5mg/1000mg tablets (boeh..	linagliptin	dpp4i
onglyza 5mg tablets (astrazeneca uk l..	saxagliptin	dpp4i
vipidia 12.5mg tablets (takeda uk ltd)	alogliptin	dpp4i
eucreas 50mg/850mg tablets (novartis ..	vildagliptin	dpp4i
jentadueto 2.5mg/850mg tablets (boehr..	linagliptin	dpp4i
vipidia 6.25mg tablets (takeda uk ltd)	alogliptin	dpp4i
canagliflozin 50mg / metformin 1g tab..	canagliflozin	sglt2i
invokana 300mg tablets (janssen-cilag..	canagliflozin	sglt2i
xigduo 5mg/850mg tablets (astrazeneca..	dapagliflozin	sglt2i
diamicron 80mg tablets (servier labor..	gliclazide	su
tolbutamide 500mg tablets	tolbutamide	su

9.4 Appendix 5: Supplementary material for chapter 5

This appendix provides the supplementary material for factors affecting prescribing paper (paper 3) presented in chapter 5 and the diagnostic code list used in the investigation of diagnostic codes.

9.4.1 5.1 Supporting Information for paper 3

Drug	*N*	*%*
Insulin	368	34.0
TZDs	290	26.8
GLP-1	286	26.45
SUs and DPP4is	55	5.1
Glinides	14	1.3
SU and insulin	14	1.3
DPP4i and insulin	11	1.0
Drug classes n<10	44	4.1
Total	1,082	

Supplementary Table 1: Drugs prescribed, other than the drug classes of interest.
Abbreviations: SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4inhibitors, TZD: Thiazolidinediones, GLP1: Glucagon-like peptide-1

		Insulin N=368	**Other combinations n=714**
Age at baseline (years)	< 30	17 (4.6)	9 (1.3)
	30 to 39	43 (11.7)	45 (6.3)
	40 to 49	53 (14.4)	139 (19.5)
	50 to 59	74 (20.1)	224 (31.4)
	60 to 69	78 (21.2)	185 (25.9)
	70 to 79	63 (17.1)	88 (12.3)
	≥80	40 (10.9)	24 (3.4)
Gender	Female	175 (47.6)	321 (45)
BMI at baseline	Underweight/normal	59 (17.2)	47 (6.7)
	Overweight	102 (29.7)	132 (18.7)
	Obese	182 (53.1)	526 (74.6)
	Missing	25 (6.8)	9 (1.3)
Ethnicity	White	160 (82.1)	394 (90.6)
	South Asian	16 (8.2)	19 (4.4)
	Black	12 (6.2)	12 (2.8)
	Other	6 (3.1)	9 (2.1)
	Mixed	n <5	n<5
	Missing	173 (47)	279 (39.1)
Patient-level index of multiple deprivation	1 LEAST deprived	40 (20.6)	62 (17.2)
	2	36 (18.6)	64 (17.7)
	3	42 (21.6)	69 (19.1)
	4	37 (19.1)	86 (23.8)
	5 MOST deprived	39 (20.1)	80 (22.2)
	Missing	174 (47.3)	353 (49.4)
Alcohol status	Non-drinker	84 (25.7)	90 (13.1)
	Ex-drinker	42 (12.8)	92 (13.4)
	Current drinker	201 (61.4)	507 (73.6)
	Missing	41 (11.1)	25 (3.5)
Smoking status	Non-smoker	145 (40.1)	259 (36.3)
	Current	72 (19.9)	138 (19.4)
	Ex-smoker	145 (40.1)	316 (44.3)
	Missing	6 (1.6)	n<5
Time taking metformin	Mean (SD)	561 (907)	1124 (1069)
HbA1c at baseline (mmol/mol)	Mean (SD)	85 (30)	77 (21)
	< 53 (7%)	29 (15.8)	45 (10.6)
	53 to 74	54 (29.5)	184 (43.2)
	>75 (9%)	100 (54.6)	197 (46.2)
	Missing	185 (50.3)	288 (40.3)
eGFR at baseline (ml/min/1.73m^2)	Mean (SD)	91 (24)	94 (19)

		Insulin N=368	Other combinations n=714
eGFR category (ml/min/1.73m^2)	< 60	27 (14.1)	40 (9.3)
	60 to 89	73 (38)	136 (31.7)
	≥ 90	92 (47.9)	253 (59)
	Missing	176 (47.8)	285 (39.9)
Diagnosis for proteinuric renal disease		7 (1.9)	14 (2)
Raised ACR at baseline		35 (35.4)	71 (23.5)
	Missing	269 (73.1)	412 (57.7)
Diagnosis for Neuropathy		33 (9)	42 (5.9)
Amputation record		5 (1.4)	11 (1.5)
Diagnosis for Retinopathy		66 (17.9)	119 (16.7)
Diagnosis for Blindness		n<5	8 (1.1)
>1 sign of microvascular disease		116 (31.5)	211 (29.6)
Systolic BP at baseline (mmHg)	Mean (SD)	130 (17)	134 (15)
	Missing	15 (4.1)	12 (1.7)
Diagnosis for CVD		69 (18.8)	77 (10.8)
Diagnosis for Heart failure		9 (2.4)	6 (0.8)
Prescription for ACEI or ARB		183 (49.7)	378 (52.9)
Prescription for statin		212 (57.6)	502 (70.3)

Supplementary Table 2: Patient demographic and lifestyle factors for people prescribed insulin or other drug options at the first stage of intensification. Numbers are N (%) unless otherwise stated. *Abbreviations: SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4inhibitors, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, HbA1c: Heamoglobin A1c, eGFR: estimated Glomerular Filtration Rate, BMI: Body mass index, BP: Blood pressure, ACEi: Angiotensin-converting-enzyme inhibitor, ARB: Angiotensin II receptor blockers, SD: Standard Deviation, ACR: Albumin creatinine ratio*

Variable	SU, Ref	DPP4i, OR (95% CI)	SGLT2i, OR (95% CI)
Age at baseline, years			
< 30	*1*	1.94 (0.86, 4.35)	4.07 (1.42, 11.67)
30-<40	*1*	0.85 (0.59, 1.22)	1.48 (0.85, 2.56)
40-<50	*1*	0.94 (0.77, 1.16)	1.81 (1.31, 2.51)
50-<60	*1*	0.86 (0.72, 1.02)	1.53 (1.16, 2.03)
60-<70	*1*	1	1
70-<80	*1*	0.93 (0.77, 1.12)	0.56 (0.36, 0.87)
80 +	*1*	0.87 (0.67, 1.14)	0.14 (0.03, 0.60)
Gender			
Male	*1*	1	1
Female	*1*	0.94 (0.83, 1.07)	1.04 (0.84, 1.29)
HbA1c at baseline (mmol/mol)			
<= 53 (7%)	*1*	1	1
53-75	*1*	1.35 (1.02, 1.79)	1.11 (0.66, 1.89)
75+ (9%)	*1*	0.70 (0.53, 0.94)	0.78 (0.46, 1.32)
eGFRat baseline (ml/min/1.73m^2)			
< 60	*1*	1	1
60-89	*1*	1.12 (0.91, 1.39)	15.45 (3.76, 63.37)
90 +	*1*	1.18 (0.93, 1.50)	16.52 (3.99, 68.29)
Time taking metformin prior to intensification (years)			
< 1	*1*	1	1
1 to <3	*1*	1.20 (1.01, 1.42)	1.48 (1.12, 1.95)
> 3	*1*	1.20 (1.02, 1.40)	1.24 (0.94, 1.64)
Diagnosis of CVD			
No CVD	*1*	1	1
CVD diagnosis	*1*	0.98 (0.83, 1.17)	0.76 (0.53, 1.09)
Diagnosis of retinopathy			
No retinopathy	*1*	1	1
Retinopathy diagnosis	*1*	0.97 (0.83, 1.14)	0.87 (0.64, 1.17)
BMI at baseline kg/m^2			
Normal/underweight	*1*	1	1
Overweight	*1*	1.10 (0.88, 1.37)	2.48 (1.21, 5.07)
Obese	*1*	1.62 (1.31, 2.00)	6.01 (3.02, 11.99)
Smoking status			
None	1	1	1
Ex	1	0.96 (0.84, 1.10)	0.90 (0.71, 1.14)
Current	1	0.91 (0.76, 1.10)	0.76 (0.56, 1.03)

Variable	SU, Ref	DPP4i, OR (95% CI)	SGLT2i, OR (95% CI)
Ethnicity			
White	*1*	1	1
South Asian	*1*	0.72 (0.57, 0.92)	0.50 (0.31, 0.81)
Black	*1*	0.59 (0.41, 0.85)	0.45 (0.23, 0.91)
Other	*1*	0.92 (0.59, 1.43)	0.48 (0.18, 1.25)
Mixed	*1*	1.29 (0.53, 3.14)	0.36 (0.04, 3.00)
Calendar time			
Early 2014	*1*	1	1
Late 2014	*1*	1.19 (0.98, 1.45)	1.73 (1.07, 2.80)
Early 2015	*1*	1.37 (1.14, 1.65)	3.02 (1.97, 4.64
Late 2015	*1*	1.72 (1.40, 2.11)	6.17 (4.02, 9.48)
Early 2016	*1*	2.31 (1.88, 2.86)	7.82 (5.09, 12.02)
Late 2016	*1*	2.35 (1.84, 2.99)	8.55 (5.41 13.50)
Early 2017	*1*	2.90 (2.20, 3.82)	15.10 (9.41, 24.61)

Supplementary Table 3 Complete case analysis. Fully adjusted odds ratios (95% CIs) for prescription of DPP4i or SGLT2i compared to SUs. Multinomial logistic regression without multiple imputation. *Abbreviations: SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4inhibitors, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, HbA1c: Heamoglobin A1c, eGFR: estimated Glomerular Filtration Rate, BMI: Body mass index*

.

Variable	SU, Ref	DPP4i, OR (95% CI)	SGLT2i, OR (95% CI)
Age at baseline, years			
< 30	*1*	1.78 (1.03, 3.10)	3.55 (1.68, 7.51)
30-<40	*1*	1.07 (0.81, 1.41)	1.26 (0.80, 1.99)
40-<50	*1*	0.98 (0.83, 1.15)	1.42 (1.10, 1.83)
50-<60	*1*	1.01 (0.88, 1.15)	1.42 (1.15, 1.76)
60-<70	*1*	1	1
70-<80	*1*	1.00 (0.86, 1.16)	0.50 (0.36, 0.70)
80 +	*1*	0.83 (0.67, 1.03)	0.12 (0.04, 0.33)
Gender			
Male	*1*	1	1
Female	*1*	0.98 (0.88, 1.09)	1.03 (0.87, 1.22)
HbA1c at baseline (mmol/mol)			
<= 53 (7%)	*1*	1	1
53-75	*1*	1.27 (0.99, 1.64)	1.32 (0.80, 2.17)
75+ (9%)	*1*	0.75 (0.5*, 0.98)	0.82 (0.50, 1.34)
eGFRat baseline (ml/min/1.73m^2)			
< 60	*1*	1	1
60-89	*1*	1.10 (0.91, 1.32)	2.85 (1.53, 5.30)
90 +	*1*	1.12 (0.92, 1.37)	3.35 (1.80, 6.23)
Time taking metformin prior to intensification (years)			
< 1	*1*	1	1
1 to <3	*1*	1.22 (1.07, 1.39)	1.54 (1.23, 1.93)
> 3	*1*	1.25 (1.10, 1.42)	1.30 (1.04, 1.63)
Diagnosis of CVD			
No CVD	*1*	1	1
CVD diagnosis	*1*	1.00 (0.87, 1.16)	0.95 (0.72, 1.27)
Diagnosis of retinopathy			
No retinopathy	*1*	1	1
Retinopathy diagnosis	*1*	1.12 (0.99, 1.28)	0.78 (0.60, 1.01)
BMI at baseline kg/m^2			
Normal/underweight	*1*	1	1
Overweight	*1*	1.28 (1.08, 1.52)	1.95 (1.21, 3.14)
Obese	*1*	1.68 (1.43, 1.99)	4.98 (3.16, 7.83)
Smoking status			
None	1	1	1
Ex	1	1.01 (0.90, 1.12)	0.92 (0.76, 1.11)
Current	1	0.99 (0.85, 1.15)	0.78 (0.60, 1.01)
Ethnicity			

Variable	SU, Ref	DPP4i, OR (95% CI)	SGLT2i, OR (95% CI)
White	*1*	1	1
South Asian	*1*	0.73 (0.59, 0.89)	0.59 (0.40, 0.86)
Black	*1*	0.64 (0.48, 0.85)	0.45 (0.24, 0.82)
Other	*1*	0.66 (0.45, 0.97)	0.52 (0.25, 1.07)
Mixed	*1*	1.01 (0.48, 2.12)	0.73 (0.15, 3.60)
Patient-level IMD			
1 LEAST deprived	*1*	1	1
2	*1*	0.95 (0.80, 1.12)	0.98 (0.73, 1.30)
3	*1*	0.95 (0.80, 1.12)	1.02 (0.76, 1.33)
4	*1*	0.79 (0.67, 0.93)	0.61 (0.46, 0.81)
5 MOST	*1*	0.99 (0.84, 1.18)	0.59 (0.44, 0.80)
Calendar time			
Early 2014	*1*	1	1
Late 2014	*1*	1.18 (1.00, 1.38)	1.80 (1.24, 2.62)
Early 2015	*1*	1.38 (1.19, 1.60)	2.70 (1.92, 3.80)
Late 2015	*1*	1.66 (1.41, 1.95)	4.43 (3.14, 6.24)
Early 2016	*1*	2.17 (1.84, 2.57)	6.99 (4.99, 9.79)
Late 2016	*1*	2.56 (2.11, 3.10)	10.42 (7.33, 14.83)
Early 2017	*1*	2.85 (2.29, 3.54)	14.73 (10.23, 21.21)

Supplementary Table 4: Results of first sensitivity analysis: Multinomial logistic regression. Model also included adjustment for patient-level IMD, England only. Multiple imputation used to account for missing data. *N= 8,217. Abbreviations: SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4inhibitors, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, HbA1c: Heamoglobin A1c, eGFR: estimated Glomerular Filtration Rate, BMI: Body mass index*

Variable	SU, Ref	DPP4i, OR (95% CI)	SGLT2i, OR (95% CI)
Age at baseline, years			
< 30	*1*	1.36 (0.85, 2.17)	2.48 (1.39, 4.40)
30-<40	*1*	1.01 (0.81, 1.26)	1.32 (0.97, 1.81)
40-<50	*1*	0.98 (0.86, 1.11)	1.27 (1.04, 1.52)
50-<60	*1*	0.98 (0.88, 1.08)	1.21 (1.04, 1.42)
60-<70	*1*	1	1
70-<80	*1*	0.96 (0.85, 1.08)	0.47 (0.37, 0.60)
80 +	*1*	0.88 (0.74, 1.04)	0.14 (0.07, 0.28)
Gender			
Male	*1*	1	1
Female	*1*	0.92 (0.85, 1)	0.99 (0.87, 1.12)
HbA1c at baseline (mmol/mol)			
<= 53 (7%)	*1*	1	1
53-75	*1*	1.41 (1.14, 1.73)	1.17 (0.79, 1.71)
75+ (9%)	*1*	0.73 (0.59, 0.90)	0.79 (0.54, 1.16)
eGFRat baseline (ml/min/1.73m^2)			
< 60	*1*	1	1
60-89	*1*	1.05 (0.90, 1.23)	5.88 (3.29, 10.50)
90 +	*1*	1.02 (0.86, 1.21)	6.77 (3.75, 12.23)
Time taking metformin prior to intensification (years)			
< 1	*1*	1	1
1 to <3	*1*	1.26 (1.13, 1.40)	1.40 (1.19, 1.64)
> 3	*1*	1.30 (1.17, 1.43)	1.23 (1.05, 1.44)
Diagnosis of CVD			
No CVD	*1*	1	1
CVD diagnosis	*1*	0.94 (0.84, 1.06)	0.95 (0.78, 1.16)
Diagnosis of retinopathy			
No retinopathy	*1*	1	1
Retinopathy diagnosis	*1*	1.09 (0.99, 1.21)	1.02 (0.86, 1.21)
BMI at baseline kg/m^2			
Normal/underweight	*1*	1	1
Overweight	*1*	1.31 (1.14, 1.51)	2.22 (1.52, 3.26)
Obese	*1*	1.72 (1.50, 1.98)	5.66 (3.93, 8.17)
Smoking status			
None	1	1	1
Ex	1	0.98 (0.90, 1.07)	1.00 (0.87, 1.15)
Current	1	0.93 (0.83, 1.05)	0.80 (0.67, 0.96)
Ethnicity			

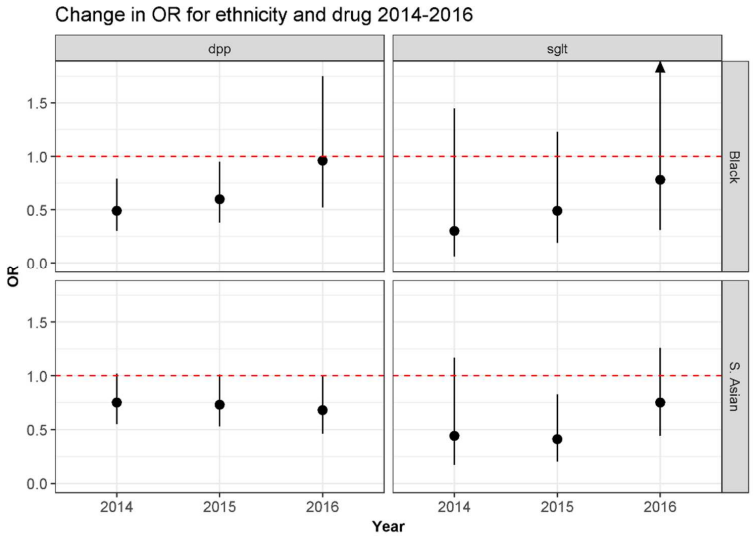
Variable	SU, Ref	DPP4i, OR (95% CI)	SGLT2i, OR (95% CI)
White	*1*	1	1
South Asian	*1*	0.70 (0.57, 0.86)	0.60 (0.42, 0.89)
Black	*1*	0.66 (0.49, 0.90)	0.55 (0.29, 1.06)
Other	*1*	0.78 (0.50, 1.24)	0.87 (0.40, 1.67)
Mixed	*1*	1.17 (0.55, 2.49)	2.05 (0.61, 6.91)
Calendar time			
Early 2014	*1*	1	1
Late 2014	*1*	1.13 (1.00, 1.29)	1.80 (1.37, 2.35)
Early 2015	*1*	1.35 (1.20, 1.53)	2.62 (2.04, 3.36)
Late 2015	*1*	1.58 (1.38, 1.80)	3.87 (3.01, 4.98)
Early 2016	*1*	2.00 (1.75, 2.29)	5.68 (4.43, 7.28)
Late 2016	*1*	2.17 (1.87, 2.52)	7.90 (6.12, 10.20)
Early 2017	*1*	2.44 (2.07, 2.88)	11.11 (8.53, 14.47)

Supplementary Table 5: Results of second sensitivity analysis: Model included individuals included individuals that were censored, or died in the 60 day after prescribing of the first intensification treatment. With multiple imputation to account for missing data. *Abbreviations: SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4inhibitors, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, HbA1c: Heamoglobin A1c, eGFR: estimated Glomerular Filtration Rate, BMI: Body mass index*

Variable	SU, Ref	DPP4i, OR (95% CI)	SGLT2i, OR (95% CI)
Age at baseline, years			
< 30	*1*	1.35 (0.85, 2.17)	2.44 (1.37, 4.34)
30-<40	*1*	1.02 (0.81, 1.27)	1.32 (0.97, 1.80)
40-<50	*1*	0.97 (0.86, 1.11)	1.26 (1.05, 1.52)
50-<60	*1*	0.97 (0.88, 1.08)	1.21 (1.04, 1.41)
60-<70	*1*	1	1
70-<80	*1*	0.97 (0.86, 1.09)	0.48 (0.38, 0.61)
80 +	*1*	0.90 (0.76, 1.07)	0.15 (0.07, 0.29)
Gender			
Male	*1*	1	1
Female	*1*	0.92 (0.85, 0.99)	0.98 (0.87, 1.11)
HbA1c at baseline (mmol/mol)			
< 54	*1*	1	1
54-75	*1*	1.34 (1.07, 1.67)	1.12 (0.77, 1.63)
75+	*1*	0.70 (0.56, 0.88)	0.77 (0.52, 1.12)
eGFR at baseline (ml/min/1.73m^2)			
< 60	*1*	1	1
60-89	*1*	1.05 (0.90, 1.22)	5.81 (3.22, 10.50)
90 +	*1*	1.00 (0.85, 1.17)	6.67 (3.68, 12.10)
Time taking metformin prior to intensification (years)			
< 1	*1*	1	1
1 to <3	*1*	1.28 (1.15, 1.42)	1.41 (1.20, 1.65)
> 3	*1*	1.34 (1.21, 1.48)	1.25 (1.07, 1.47)
Diagnosis of CVD			
No CVD	*1*	1	1
CVD diagnosis	*1*	0.95 (0.85, 1.06)	0.95 (0.78, 1.17)
Microvascular disease			
No markers	*1*	1	1
One marker		0.94 (0.86, 1.02)	0.94 (0.81, 1.08)
Two or more markers	*1*	0.96 (0.81, 1.14)	0.80 (0.58, 1.10)
BMI at baseline kg/m^2			
Normal/underweight	*1*	1	1
Overweight	*1*	1.30 (1.12, 1.50)	2.22 (1.51, 3.25)
Obese	*1*	1.70 (1.48, 1.95)	5.61 (3.89, 8.12)
Smoking status			
None	1	1	1
Ex	1	0.99 (0.91, 1.08)	1.00 (0.87, 1.15)
Current	1	0.94 (0.84, 1.06)	0.81 (0.68, 0.97)
Ethnicity			
White	*1*	1	1
South Asian	*1*	0.71 (0.58, 0.87)	0.60 (0.42, 0.85)

Variable	SU, Ref	DPP4i, OR (95% CI)	SGLT2i, OR (95% CI)
Black	*1*	0.69 (0.50, 0.94)	0.54 (0.30, 0.96)
Other	*1*	0.78 (0.53, 1.14)	0.86 (0.39, 1.90)
Mixed	*1*	1.15 (0.48, 2.73)	2.11 (0.60, 7.47)
Calendar time			
Early 2014	*1*	1	1
Late 2014	*1*	1.13 (1.00, 1.29)	1.80 (1.37, 2.35)
Early 2015	*1*	1.36 (1.20, 1.53)	2.61 (2.04, 3.36)
Late 2015	*1*	1.58 (1.39, 1.80)	3.86 (3.00, 4.98)
Early 2016	*1*	1.99 (1.74, 2.28)	5.64 (4.40, 7.23)
Late 2016	*1*	2.16 (1.86, 2.50)	7.88 (6.11, 10.17)
Early 2017	*1*	2.42 (2.05, 2.85)	10.95 (8.41, 14.27)

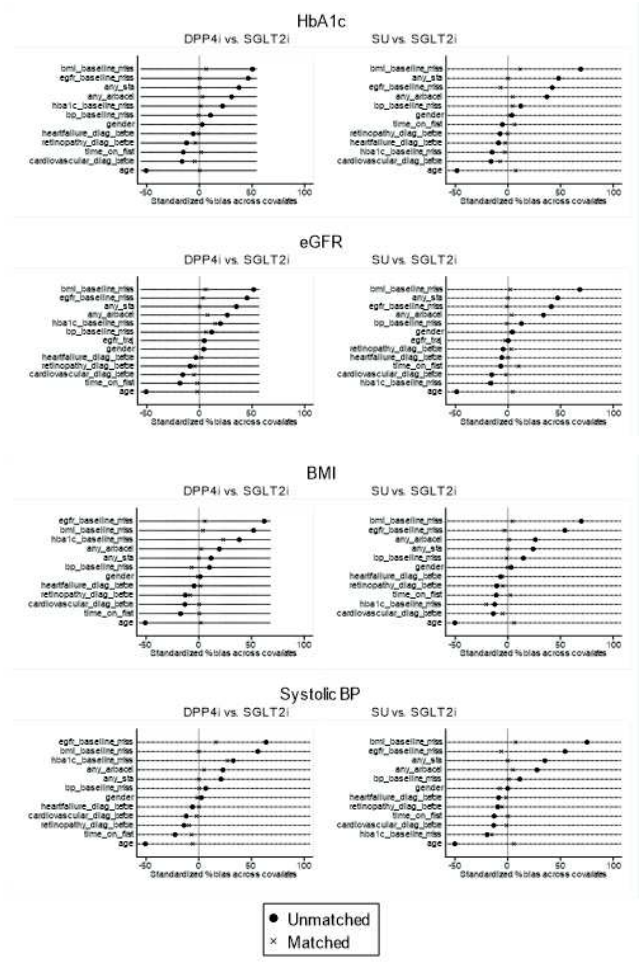
Supplementary table 6: Results of third sensitivity analysis: Replaced retinopathy with a count of microvascular disease markers. With multiple imputation to account for missing data. *Abbreviations: SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4inhibitors, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, HbA1c: Heamoglobin A1c, eGFR: estimated Glomerular Filtration Rate, BMI: Body mass index*



Supplementary Fig 1 Repeated the primary analysis for each individual year 2014-2016 (excluding time as a covariate), and compared ORs for different ethnicity (South Asian and Black)

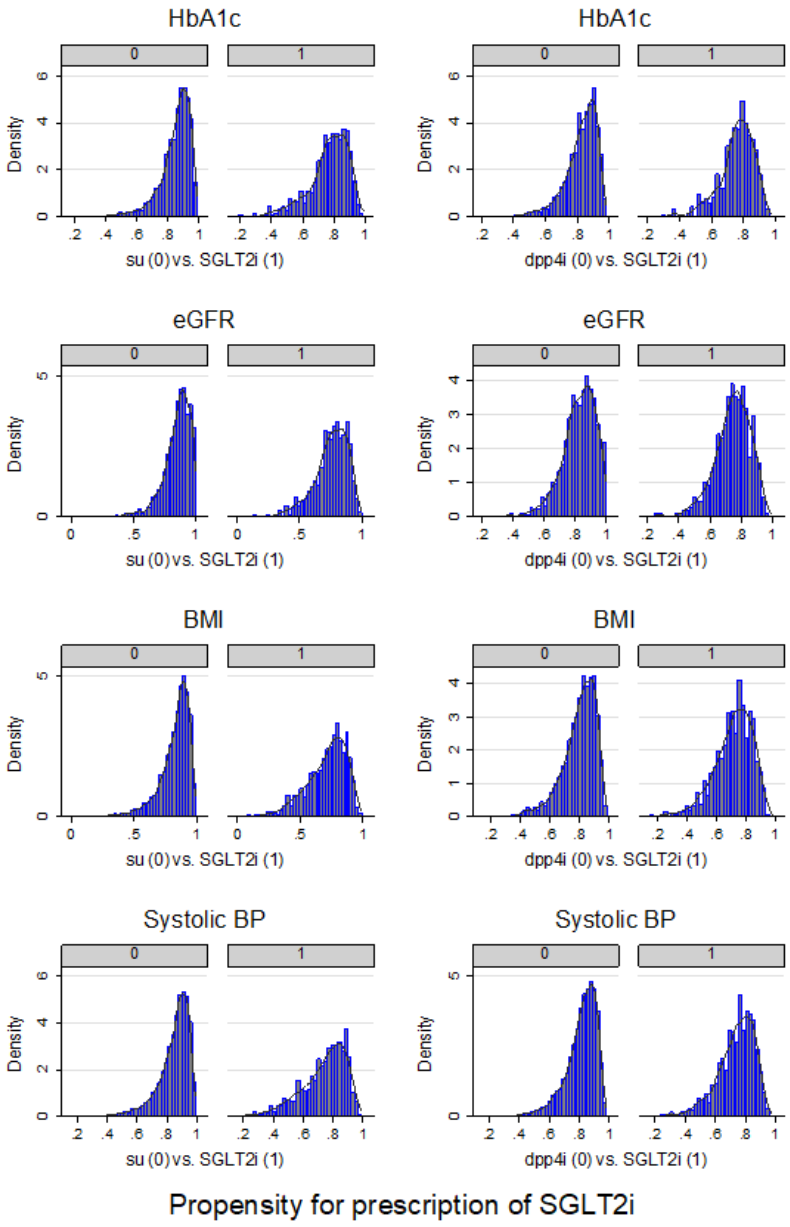
9.5 Appendix 6: Supplementary material for chapter 6

9.5.1 Supplementary files for paper 6



Supplementary Figure 1: Standardised mean % differences in baseline characteristics for each cohort, unadjusted and compared to the final selected weighted matched sample

Where hba1c_baseline_miss, egfr_baseline_miss, bmi_baseline_miss and bp_baseline_miss are the baseline measures, after accounting for missingness in the variables. egfr_traj: eGFR trajectory, time_on_first: time taking metformin prior to changing drug, cardiovascular_diag_before and retinopathy_diag_before are indicators of cardiovascular disease and retinopathy respectively. any_arb and any_sta are indicators of prescriptions for ARB or statins prior to baseline. imd_pt: patient-level index of multiple deprivation



Supplementary Figure 2: Propensity score for SGLT2i for each measure of interest, in final selected PS model.

Measure	Number of SGLT2is available	Number of unmatched SGLT2is	Mean of measure in unmatched	DPP4i contrast PS for SGLT2i Mean (SD)	SU contrast PS for SGLT2i Mean (SD)
eGFR	483	21	94.0	0.52 (0.12)	0.45 (0.13)
HbA1c	516	35	75.2	0.54 (0.11)	0.49 (0.11)
BMI	764	26	43.9	0.47 (0.15)	0.45 (0.17)
Sys BP	824	88	136.1	0.54 (0.11)	0.49 (0.14)

Supplementary Table 1: Description of unmatched SGLT2is

Measure	Mean number of SU matches	Mean number of DPP4i matches
eGFR	3.53	2.97
HbA1c	3.52	3.00
BMI	2.92	2.66
Sys BP	3.47	2.97

Supplementary Table 2: Number of matches found for each treatment group (Aim was for 5:1:4 SU:SGLT2i:DPP4i)

	Length of follow-up	Mean number of measures for analysis cohort		
	Days, mean (median)	DPP4i	SGLT2i	SU
eGFR	616 (582)	5.5	5.4	6.1
HbA1c	605 (572)	5.5	5.1	5.8
BMI	624 (590)	5.4	5.6	5.5
Systolic BP	617 (582)	7.1	6.5	7.5

Supplementary Table 3: Length of follow-up (days) and number of repeated measures available for each analysis cohort

	Category	SU	SGLT2i	DPP4i
Counts		1630	462	1374
Age at baseline	**Years**	55.8 (10.9)	56 (10.3)	56.4 (10.8)
BMI baseline	**kg/m^2**	34.9 (5.9)	35 (5.7)	34.9 (5.7)
eGFR baseline	**ml/min/1.73m^2**	95 (13.8)	94.8 (13.2)	94.7 (13.6)
Systolic BP at baseline	**mmHg**	133.8 (13.3)	134.1 (12.6)	133.8 (13.3)
HbA1c at baseline	**mmol/mol**	76.1 (17.6)	75.9 (16.1)	76 (16.2)
Time taking metformin prior to intensification	**Month**	36.1 (34.8)	37.7 (32.6)	38.1 (34.4)
Gender	**Female, n (%)**	179 (39)	189 (41)	179 (39)
Diagnosis of CVD	**n (%)**	51 (11)	45 (10)	45 (10)
Diagnosis of HF	**n (%)**	15 (3)	14 (3)	10 (2)
Diagnosis of retinopathy	**n (%)**	75 (16)	75 (16)	88 (19)
Prescription for ARB or ACE inhibitor	**n (%)**	243 (53)	273 (59)	246 (53)
Prescription for statin	**n (%)**	319 (69)	324 (70)	343 (74)
Patient-level index of multiple deprivation	**1 LEAST deprived**	47 (10)	48 (10)	47 (10)
	2	45 (10)	47 (10)	43 (9)
	3	60 (13)	58 (13)	59 (13)
	4	43 (9)	41 (9)	40 (9)
	5 MOST deprived	40 (9)	32 (7)	37 (8)
	Missing category	228 (49)	236 (51)	237 (51)
Smoking status	**Non-smoker**	180 (39)	178 (39)	178 (39)
	Current	80 (17)	72 (16)	69 (15)
	Ex-smoker	200 (43)	212 (46)	215 (47)
	Missing category	<5	<5	<5
Ethnicity n (%)	**White**	191 (41)	193 (42)	189 (41)
	South Asian	12 (3)	10 (2)	9 (2)
	Black	8 (2)	7 (2)	7 (2)
	Other	1 (0)	1 (0)	0 (0)
	Mixed	1 (0)	2 (0)	1 (0)
	Missing category	249 (54)	249 (54)	255 (55)

Supplementary Table 4: Baseline characteristics for final weighted matched sample for eGFR

After iteration of the propensity score model, the following covariates were included in the model: age, HbA1c, eGFR, eGFR^2, BMI, systolic BP, patient-level IMD, ethnicity. The group was further matched on quintiles of baseline eGFR % is of entire cohort.

	Category	SU	SGLT2i	DPP4i
Count		**2158**	**738**	**1960**
Age at baseline	**Years**	55.6 (11.5)	55.2 (10.1)	56.1 (10.6)
BMI baseline	**kg/m²**	36.6 (6.2)	36.4 (6.5)	36.4 (6.2)
eGFR baseline	**ml/min/1.73m²**	92.8 (12.8)	92.6 (9.9)	92.1 (11.2)
Systolic BP at baseline	**mmHg**	134.1 (13.5)	134 (13.4)	134 (13.1)
HbA1c at baseline	**mmol/mol**	76.8 (14.1)	76.5 (12.4)	75.9 (11.8)
Time taking metformin prior to intensification	**Month**	36.2 (35.1)	36.4 (33.2)	37.1 (34.2)
Gender	**Female, n (%)**	325 (44)	303 (41)	316 (43)
Diagnosis of CVD	**n (%)**	85 (11)	73 (10)	77 (10)
Diagnosis of HF	**n (%)**	20 (3)	15 (2)	17 (2)
Diagnosis of retinopathy	**n (%)**	127 (17)	111 (15)	123 (17)
Prescription for ARB or ACE inhibitor	**n (%)**	412 (56)	419 (57)	408 (55)
Prescription for statin	**n (%)**	505 (68)	516 (70)	559 (76)
Patient-level index of multiple deprivation	**1 LEAST deprived**	57 (8)	60 (8)	58 (8)
	2	60 (8)	57 (8)	58 (8)
	3	76 (10)	72 (10)	70 (10)
	4	69 (9)	58 (8)	65 (9)
	5 MOST deprived	54 (7)	48 (7)	45 (6)
	Missing category	421 (57)	443 (60)	442 (60)
Smoking status	**Non-smoker**	285 (39)	284 (38)	279 (38)
	Current	129 (18)	113 (15)	124 (17)
	Ex-smoker	322 (44)	341 (46)	334 (45)
	Missing category	<5	<5	<5
Ethnicity	**White**	313 (42)	306 (41)	310 (42)
n (%)	**South Asian**	21 (3)	19 (3)	14 (2)
	Black	8 (1)	6 (1)	7 (1)
	Other	2 (0)	2 (0)	2 (0)
	Mixed	2 (0)	2 (0)	2 (0)
	Missing category	392 (53)	403 (55)	403 (55)

Supplementary Table 5: Baseline characteristics for final weighted matched sample for BMI

After iteration of the propensity score model, the following covariates were included in the model: age, HbA1c, eGFR, BMI, BMI2, systolic BP, patient-level IMD, ethnicity. The groups were further matched on centiles of baseline BMI. % is of entire cohort.

	Category	SU	SGLT2i	DPP4i
Counts		2554	736	2186
Age at baseline	**Years**	56.6 (11.5)	56.5 (9.8)	56.5 (10.6)
BMI baseline	**kg/m^2**	34.7 (5.5)	35.1 (5.5)	34.7 (5.4)
eGFR baseline	**ml/min/1.73m^2**	91.6 (12.7)	91.5 (9.6)	91.2 (11)
Systolic BP at baseline	**mmHg**	134.5 (14.4)	134.4 (14)	134.4 (14.1)
HbA1c at baseline	**mmol/mol**	76 (13)	75.8 (12.1)	75.5 (11.4)
Time taking metformin prior to intensification	**Month**	37.2 (35.3)	36.5 (32.4)	38.1 (34.3)
Gender	**Female, n (%)**	305 (41)	295 (40)	283 (38)
Diagnosis of CVD	**n (%)**	92 (13)	80 (11)	82 (11)
Diagnosis of HF	**n (%)**	21 (3)	17 (2)	17 (2)
Diagnosis of retinopathy	**n (%)**	119 (16)	107 (15)	128 (17)
Prescription for ARB or ACE inhibitor	**n (%)**	414 (56)	438 (60)	407 (55)
Prescription for statin	**n (%)**	514 (70)	517 (70)	555 (75)
Patient-level index of multiple deprivation	**1 LEAST deprived**	65 (9)	64 (9)	59 (8)
	2	59 (8)	56 (8)	55 (7)
	3	75 (10)	76 (10)	76 (10)
	4	60 (8)	60 (8)	59 (8)
	5 MOST deprived	53 (7)	55 (7)	54 (7)
	Missing category	425 (58)	425 (58)	433 (59)
Smoking status	**Non-smoker**	282 (38)	293 (40)	276 (37)
	Current	125 (17)	113 (15)	118 (16)
	Ex-smoker	327 (44)	330 (45)	342 (47)
	Missing category	<5	<5	<5
Ethnicity	**White**	298 (41)	291 (40)	295 (40)
n (%)	**South Asian**	16 (2)	19 (3)	17 (2)
	Black	9 (1)	9 (1)	9 (1)
	Other	<5	<5	<5
	Mixed	<5	<5	<5
	Missing category	410 (56)	412 (56)	410 (56)

Supplementary Table 6: Baseline characteristics for final weighted matched sample for Systolic BP

After iteration of the propensity score model, the following covariates were included in the model: age, HbA1c, eGFR, BMI, systolic BP, patient-level IMD, ethnicity. The groups were further matched on 20 groups of baseline systolic BP. % is of entire cohort.

		HbA1c (*mmol/mol*)			*eGFR (ml/min/1.73m²)*		
	Week:	**0**	**12**	**60**	**0**	**12**	**60**
SU	**Absolute value**	**76.7 (75.8-77.5)**	**62.3 (61.2-63.5)**	**62.9 (61.4-64.4)**	**95.0 (94.3-95.8)**	**95.5 (94.4-96.5)**	**93.0 (91.8-94.2)**
	Change from baseline		**-14.3 (-15.5, -13.2)**	**-13.8 (-15.4, -12.2)**		**0.5 (-0.4, 1.3)**	**-2.0 (-2.9, -1.1)**
SGLT2i	**Absolute value**	**76.4 (74.9-77.9)**	**61.2 (59.7-62.8)**	**60.3 (57.9-62.8)**	**94.8 (93.6-96.0)**	**91.8 (90.2-93.3)**	**92.7 (90.9-94.5)**
	Change from baseline		**-15.2 (-16.9, -13.5)**	**-16.1 (-18.7, -13.5)**		**-3.1 (-4.1, -2.0)**	**-2.2 (-3.6, -0.7)**
DPP4i	**Absolute value**	**76.7 (75.7-77.6)**	**64.8 (63.5-66.1)**	**66.9 (65.0-68.8)**	**94.7 (93.9-95.4)**	**93.6 (92.6-94.7)**	**92.8 (91.6-93.9)**
	Change from baseline		**-11.9 (-13.1, -10.6)**	**-9.8 (-11.6, -7.9)**		**-1.0 (-1.9, -0.2)**	**-1.9 (-2.9, -1.0)**

		BMI (kg/m²)			*Systolic BP (mmHg)*		
	Week:	**0**	**12**	**60**	**0**	**12**	**60**
SU	**Absolute value**	**36.6 (36.2-37.0)**	**36.6 (36.1-37.0)**	**36.8 (36.4-37.2)**	**134.5 (133.9-135.2)**	**133.8 (132.7-134.9)**	**134.8 (133.6-135.9)**
	Change from baseline		**0.0 (-0.3, 0.2)**	**0.2 (0.0, 0.4)**		**-0.8 (-1.9, -0.4)**	**0.2 (-1.0, 1.4)**
SGLT2i	**Absolute value**	**36.4 (35.9-36.8)**	**35.7 (35.2-36.2)**	**34.6 (34.1-35.2)**	**134.4 (133.4-135.4)**	**132.1 (130.7-133.5)**	**131.8 (130.2-133.5)**
	Change from baseline		**-0.7 (-0.9, -0.5)**	**-1.7 (-2.1, -1.4)**		**-2.3 (-3.8, -0.8)**	**-2.6 (-4.4, -0.8)**
DPP4i	**Absolute value**	**36.4 (36.1-36.8)**	**36.1 (35.8-36.5)**	**35.7 (35.3-36.1)**	**134.4 (133.7-135.0)**	**133.4 (132.3-134.6)**	**133.4 (132.2-134.6)**
	Change from baseline		**-0.3 (-0.5, -0.1)**	**-0.8 (-1.0, -0.6)**		**-0.9 (-2.1, 0.2)**	**-0.9 (-2.1, 0.3)**

Supplementary Table 7. Mean (95% confidence intervals) absolute values and change from baseline for clinical variables at baseline, 12, and 60 weeks, for propensity score matched cohorts of individuals following intensification with DPP4i, SGLT2i and SU after metformin monotherapy. Abbreviations: SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4 inhibitors, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, HbA1c: Haemoglobin A1c, eGFR: estimated glomerular filtration rate, BMI: Body mass index, BP: Blood pressure.

	Mean HbA1c	N	Mean HbA1c	N	Mean HbA1c	N	Mean HbA1c	N	Mean HbA1c	N	Mean HbA1c	N	Mean HbA1c	N
Week:	0	0	12	12	24	24	36	36	48	48	60	60	72	72
DPP4i	76.66	1445	76.35	1396	75.64	1271	75.36	1122	75.32	991	75.00	868	74.81	740
SGLT2i	76.43	481	76.33	470	76.24	409	76.27	355	76.69	305	77.19	260	77.09	213
SU	76.66	1691	76.55	1657	76.25	1558	76.17	1443	75.94	1330	75.65	1204	75.65	1071

Supplementary Table 8: Impact of attrition through patients leaving the cohort on HbA1c (mmol/mol). At each time point the mean values represent the BASELINE weighted mean values of HbA1c for participants (and numbers) still contributing data over time for the HbA1c cohort.

	Mean eGFR	N	Mean eGFR	N	Mean eGFR	N	Mean eGFR	N	Mean eGFR	N	Mean eGFR	N	Mean eGFR	N
Week:	0	0	12	12	24	24	36	36	48	48	60	60	72	72
DPP4i	94.68	1374	94.59	1334	94.56	1228	94.65	1087	94.36	978	94.56	853	94.31	728
SGLT2i	94.83	462	94.94	456	95.23	410	95.24	362	95.21	310	95.51	266	95.58	223
SU	95.00	1630	95.07	1608	95.09	1523	95.03	1414	94.97	1315	94.95	1175	94.60	1034

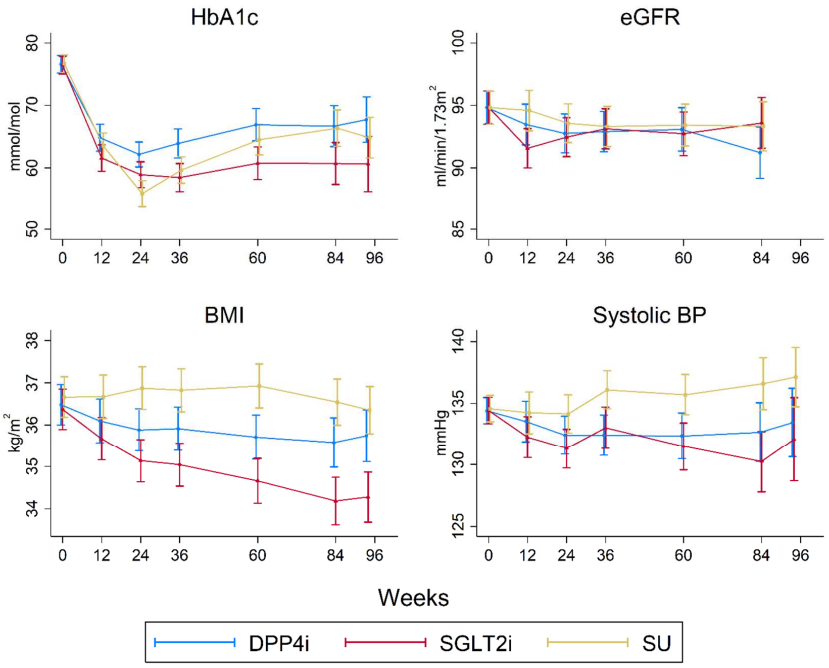
Supplementary Table 9: Impact of attrition through patients leaving the cohort on eGFR (ml/min/1.73m^2). At each time point the mean values represent the BASELINE weighted mean values of eGFR for participants (and numbers) still contributing data over time for the eGFR cohort.

	Mean BMI	N	Mean BMI	N	Mean BMI	N	Mean BMI	N	Mean BMI	N	Mean BMI	N	Mean BMI	N
Week	0	0	12	12	24	24	36	36	48	48	60	60	72	72
DPP4i	36.45	1960	36.40	1921	36.33	1763	36.29	1610	36.14	1442	35.98	1242	36.07	1041
SGLT2i	36.37	738	36.33	715	36.30	638	36.18	558	36.15	489	36.22	427	36.51	348
SU	36.60	2158	36.57	2117	36.56	2006	36.50	1883	36.45	1763	36.40	1580	36.28	1419

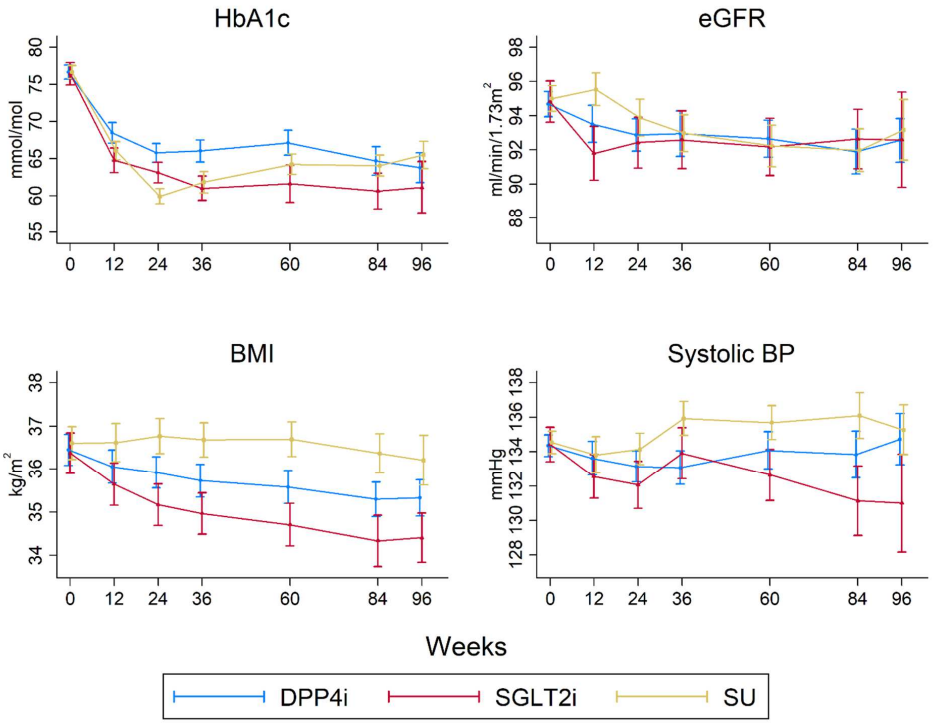
Supplementary Table 10: Impact of attrition through patients leaving the cohort on BMI (kg/m^2). At each time point the mean values represent the BASELINE weighted mean values of BMI for participants (and numbers) still contributing data over time for the BMI cohort.

	Mean BP	N	Mean BP	N	Mean BP	N	Mean BP	N	Mean BP	N	Mean BP	N	Mean BP	N
Week	0	0	12	12	24	24	36	36	48	48	60	60	72	72
DPP4i	134.4	2186	134.2	2134	134.0	1962	133.9	1771	134.2	1577	134.0	1355	133.8	1143
SGLT2i	134.4	736	134.3	718	134.1	641	133.7	562	133.8	487	133.8	427	133.5	345
SU	134.5	2554	134.4	2496	134.3	2352	134.3	2190	134.5	2042	134.5	1840	134.4	1634

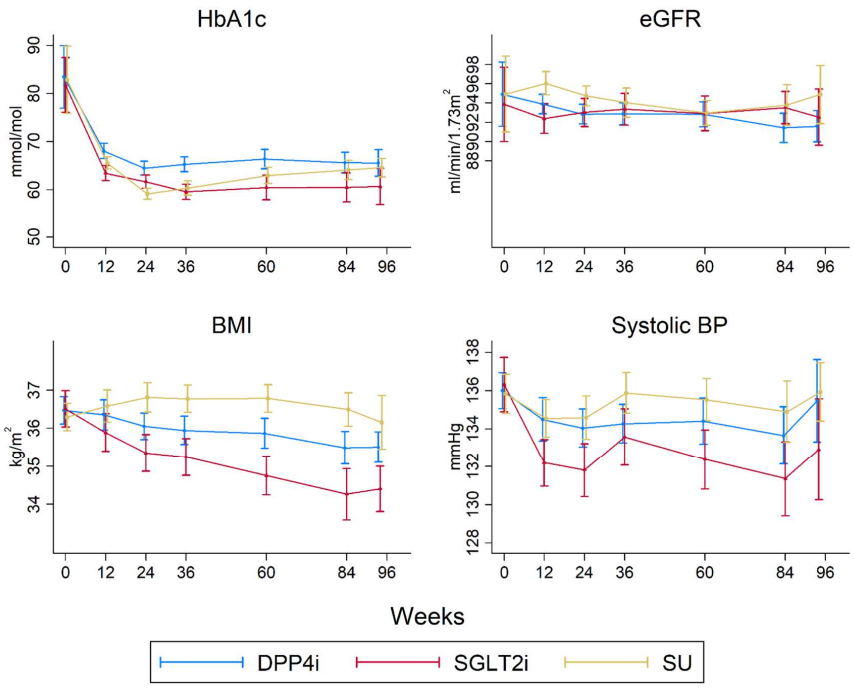
Supplementary Table 11: Impact of attrition through patients leaving the cohort on systolic BP (mmHg). At each time point the mean values represent the BASELINE weighted mean values of systolic BP for participants (and numbers) still contributing data over time for the systolic BP cohort.



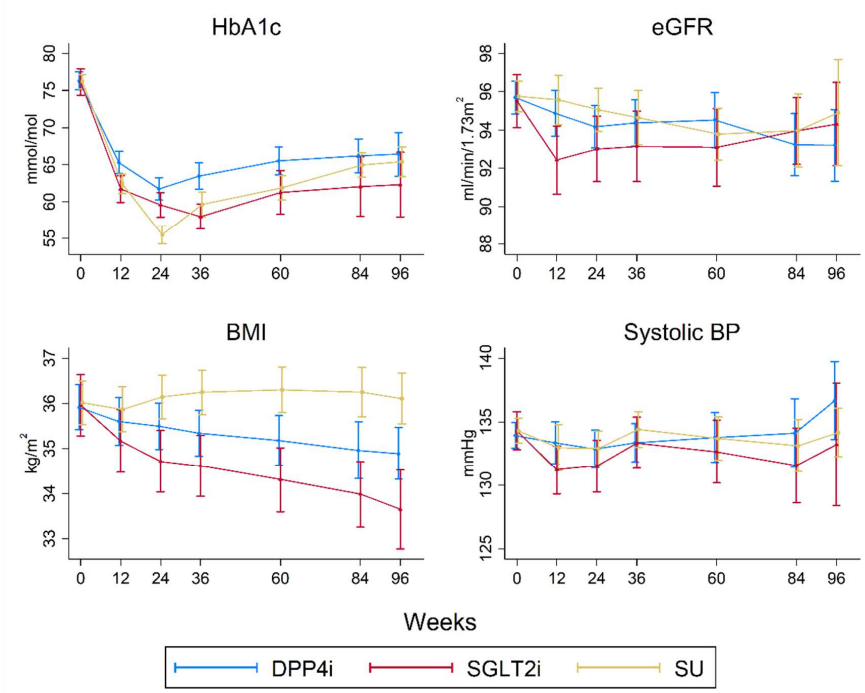
Supplementary Figure 3: Mean (95% confidence intervals) of each clinical measure during treatment for 1:1:1 matched propensity score matched cohorts of individuals following intensification with DPP4i, SGLT2i and SU after metformin monotherapy



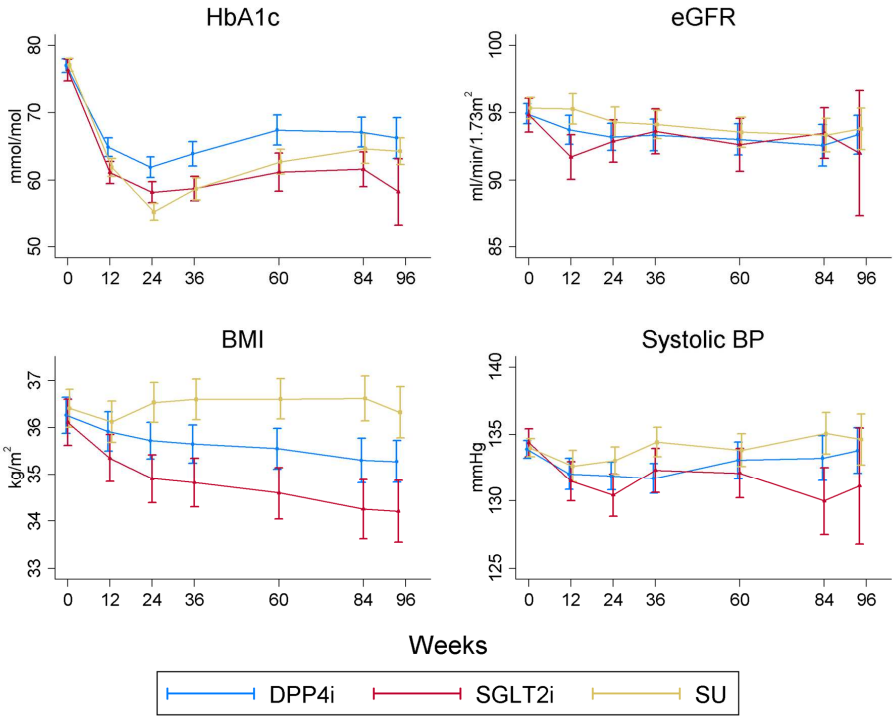
Supplementary Figure 4: Mean (95% confidence intervals) of each clinical measure during treatment, for propensity score matched cohorts of individuals (intention to treat model), following intensification with DPP4i, SGLT2i and SU after metformin monotherapy



Supplementary Figure 5: Mean (95% confidence intervals) of each clinical measure during treatment, for propensity score matched cohorts of individuals with missing data handled using multiple imputation, following intensification with DPP4i, SGLT2i and SU



Supplementary Figure 6: Mean (95% confidence intervals) of each clinical measure during treatment, for a propensity score matched cohort of individuals (using only individuals with baseline and follow-up measures for all of eGFR, HbA1c, BMI and BP), following intensification with DPP4i, SGLT2i and SU after metformin monotherapy



Supplementary Figure 7: Mean (95% confidence intervals) of each clinical measure during treatment, primary analysis repeated excluding individuals in the top 25th percentile for the number of tests available during follow-up (eGFR, HbA1c, BMI and BP), following intensification with DPP4i, SGLT2i and SU after metformin monotherapy

Measure	SU		SGLT2i		DPP4i	
Week:	12	60	12	60	12	60
HbA1c *mmol/mol*	66.1 (64.8 - 67.3)	64.2 (62.9 - 65.6)	64.8 (63.1 - 66.4)	61.6 (59.1 - 64.1)	68.5 (67.1 - 69.9)	67.1 (65.5 - 68.8)
eGFR *ml/min/1.73m²*	95.5 (94.6 - 96.5)	92.2 (91.0 - 93.5)	91.8 (90.2 - 93.4)	92.2 (90.5 - 93.9)	93.5 (92.4 - 94.6)	92.7 (91.6 - 93.7)
BMI *kg/m²*	36.6 (36.2 - 37.1)	36.7 (36.3 - 37.1)	35.6 (35.2 - 36.1)	34.7 (34.2 - 35.2)	36.1 (35.7 - 36.4)	35.6 (35.2 - 36.0)
Systolic BP *mmHg*	133.8 (132.8 - 134.9)	135.7 (134.7 - 136.7)	132.6 (131.3 - 133.8)	132.6 (131.2 - 134.1)	133.6 (132.6 - 134.6)	134.1 (133.0 - 135.2)

Supplementary table 12: Mean HbA1c, eGFR, BMI and systolic BP and 95% CI at 12 and 60 weeks for SU, SGLT2i and DPP4i treatment cohorts, intention to treat analysis

	EMPA-REG (2)	CANVAS (3)	DECLARE-TIMI (4)	CREDENCE (5)	Current study**
Mean age (years)	63	63	64	63	56
Female (%)	28	36	37	34	40
Mean HbA1c (mmol/mol)#	65	66	67	67	76
Mean Systolic BP (mmHg)	135	136	135	140	134
Mean BMI (kg/m^2)	31	32	32	31	34
Mean eGFR (mls/min/1.73m^2)	74	77	86	56	92
Cardiovascular disease (%)	98.9[c]	65.6	40.8	50.4	11
Retinopathy (%)		21		43	16
Heart failure (%)	10.1	14.4	10.0	14.8	2
Concomitant medications					
Prevalent metformin users	74	77	82	58[a]	100
ACE Inhibitor users	80	80[†]	81[$]	100[†]	54[$]
Statin users	76	75	75[b]	69	73

Supplementary Table 13: Comparison of individuals included in our HbA1c matched analysis to individuals included in main SGLT2 inhibitor cardiovascular outcome trials. (56, 57, 140, 165)

Where studies have not provided overall means or percentage, we have provided the placebo group statistics. #converted from % if data not given, **For HbA1c matched cohort, [a] biguanides, [†]Renin-angiotensin-aldosterone system inhibitors, [$]ACE Inhibitors or Angiotensin receptor blockers, [b] Statin or ezetimibe, [c] Cardiovascular risk factors (includes coronary artery disease, history of myocardial infarction, coronary artery bypass graft, history of stroke, peripheral artery disease, coronary artery disease and cardiac failure)

Abbreviations: SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4 inhibitors, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, HbA1c: Haemoglobin A1c, eGFR: estimated glomerular filtration rate, BMI: Body mass index, BP: Blood pressure, ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin 2 receptor blockers.

	Category	SU	SU Original cohort	SGLT2i	SGLT2i original cohort	DPP4i	DPP4i original cohort
Counts		2,521	5,010	704	1,187	2,339	4,434
Age at baseline	**Years**	60.2 (12.6)	61 (13)	55 (10.3)	55 (10)	60.4 (12.3)	61 (12)
BMI baseline	**kg/m2**	31.9 (6.2)	32 (6)	36.9 (7.0)	37 (7)	33.2 (6.4)	33 (7)
eGFR baseline	**ml/min/1.73m2**	89.6 (10.3)	89 (18)	96.4 (7.0)	96 (13)	88.8 (9.8)	88 (18)
Systolic BP at baseline	**mmHg**	132.9 (12.0)	133 (14)	134.2 (12.1)	134 (14)	133.7 (11.8)	133 (14)
HbA1c at baseline	**mmol/mol**	80.2 (12.0)	80 (21)	77.1 (10.2)	77 (17)	73 (9.0)	73 (16)
Time taking metformin prior to intensification	**Month**	39.9 (36.3)	40 (37)	35.9 (33.7)	36 (33)	43.9 (36.7)	44 (37)
Gender	**Female, n (%)**	993 (39)	1988 (39.7)	271 (38)	474 (39.9)	904 (39)	1745 (39.4)
Diagnosis of CVD	**n (%)**	351 (14)	707 (14.1)	74 (11)	119 (10)	298 (13)	601 (13.6)
Diagnosis of HF	**n (%)**	89 (4)	194 (3.9)	9 (1)	24 (2)	68 (3)	146 (3.3)
Diagnosis of retinopathy	**n (%)**	411 (16.0)	868 (17.3)	101 (14)	181 (15.2)	442 (19)	861 (19.4)
Prescription for ARB or ACE inhibitor	**n (%)**	1361 (54.0)	2711 (54.1)	386 (55)	670 (56.4)	1301 (56)	2490 (56.2)
Prescription for statin	**n (%)**	1752 (69.0)	3530 (70.5)	483 (69)	819 (69)	1768 (76)	3387 (76.4)
Patient-level index of multiple deprivation	**1 LEAST deprived**	208 (8)	467 (9.3)	44 (6)	93 (7.8)	163 (7)	398 (9.0)
	2	230 (9)	485 (9.7)	50 (7)	99 (8.3)	156 (7)	378 (8.5)
	3	267 (11)	567 (11.3)	54 (8)	117 (9.9)	197 (8)	449 (10.1)
	4	338 (13)	643 (12.8)	57 (8)	99 (8.3)	215 (9)	427 (9.6)
	5 MOST deprived	280 (11)	589 (11.8)	49 (7)	81 (6.8)	224 (10)	479 (10.8)
	Missing category	1198 (48)	2259 (45.1)	450 (64)	698 (58.8)	1384 (59)	2303 (51.9)
Smoking status	**Non-smoker**	923 (37)	1883 (37.6)	274 (39)	462 (38.9)	866 (37)	1642 (37.0)
	Current	426 (17)	818 (16.3)	116 (16)	193 (16.3)	394 (17)	688 (15.5)
	Ex-smoker	1165 (46)	2297 (45.8)	314 (45)	532 (44.8)	1078 (46)	2102 (47.4)
	Missing category	7 (0)	12 (0.2)	<5	N<5	<5	N<5
Ethnicity	**White**	1040 (41)	2052 (41.5)	297 (42)	500 (42.1)	1053 (45)	1944 (43.8)
n (%)	**South Asian**	114 (5)	229 (4.6)	21 (3)	31 (2.6)	73 (3)	146 (3.3)
	Black	63 (2)	122 (2.4)	<5	9 (0.8)	32 (1)	61 (1.4)
	Other	35 (1)	59 (1.2)	<5	5 (0.4)	10 (0)	26 (0.6)
	Mixed	9 (0)	14 (0.3)	<5	N<5	7 (0)	16 (0.4)
	Missing category	1260 (50)	2534 (50.6)	380 (54)	640 (53.9)	1164 (50)	2241 (50.5)
Year started	**2014**	957 (38)	2090 (41.7)	125 (18)	217 (18.3)	670 (29)	1390 (31.3)
follow-up	**2015**	828 (33)	1668 (33.3)	195 (28)	355 (29.9)	689 (29)	1453 (32.8)
n (%)	**2016**	536 (21)	989 (19.7)	245 (35)	444 (37.4)	664 (28)	1207 (27.2)
	2017	200 (8)	263 (5.2)	139 (20)	171 (14.4)	316 (14)	384 (8.7)

Supplementary Table 14: Characteristics for people dropped from the eGFR sample due to missing baseline values and/or follow-up values. Compared to the study population at baseline for individuals intensifying treatment from metformin monotherapy with SU, SGLT2i or DPP4i between 2014-2017 (Table 1)

	Category	SU	SU Original cohort	SGLT2i	SGLT2i original cohort	DPP4i	DPP4i original cohort
Counts		2358	5,010	671	1,187	2210	4,434
Age at baseline	**Years**	60.5 (12.8)	61 (13)	55.1 (10.5)	55 (10)	60.6 (12.4)	61 (12)
BMI baseline	**kg/m2**	31.9 (6.2)	32 (6)	37 (7.2)	37 (7)	33.1 (6.3)	33 (7)
eGFR baseline	**ml/min/1.73m2**	89.1 (10.2)	89 (18)	96.1 (6.9)	96 (13)	88.1 (10.3)	88 (18)
Systolic BP at baseline	**mmHg**	132.9 (12.2)	133 (14)	134.3 (12.1)	134 (14)	133.7 (11.8)	133 (14)
HbA1c at baseline	**mmol/mol**	79.8 (10.3)	80 (21)	76.6 (9.3)	77 (17)	72.9 (8.5)	73 (16)
Time taking metformin prior to intensification	**Month**	40.1 (36.7)	40 (37)	35.6 (32.9)	36 (33)	44.6 (37.4)	44 (37)
Gender	**Female, n (%)**	932 (40)	1988 (39.7)	259 (39)	474 (39.9)	847 (38)	1745 (39.4)
Diagnosis of CVD	**n (%)**	341 (14)	707 (14.1)	74 (11)	119 (10)	291 (13)	601 (13.6)
Diagnosis of HF	**n (%)**	91 (4)	194 (3.9)	12 (2)	24 (2)	73 (3)	146 (3.3)
Diagnosis of retinopathy	**n (%)**	382 (16)	868 (17.3)	101 (15)	181 (15.2)	412 (19)	861 (19.4)
Prescription for ARB or ACE inhibitor	**n (%)**	1306 (55)	2711 (54.1)	369 (55)	670 (56.4)	1235 (56)	2490 (56.2)
Prescription for statin	**n (%)**	1652 (70)	3530 (70.5)	458 (68)	819 (69)	1677 (76)	3387 (76.4)
Patient-level index of multiple deprivation	**1 LEAST deprived**	174 (7)	467 (9.3)	39 (6)	93 (7.8)	141 (6)	398 (9.0)
	2	219 (9)	485 (9.7)	44 (7)	99 (8.3)	139 (6)	378 (8.5)
	3	243 (10)	567 (11.3)	52 (8)	117 (9.9)	174 (8)	449 (10.1)
	4	316 (13)	643 (12.8)	58 (9)	99 (8.3)	198 (9)	427 (9.6)
	5 MOST deprived	261 (11)	589 (11.8)	43 (6)	81 (6.8)	206 (9)	479 (10.8)
	Missing category	1145 (49)	2259 (45.1)	435 (65)	698 (58.8)	1352 (61)	2303 (51.9)
Smoking status	**Non-smoker**	885 (38)	1883 (37.6)	247 (37)	462 (38.9)	820 (37)	1642 (37.0)
	Current	395 (17)	818 (16.3)	115 (17)	193 (16.3)	378 (17)	688 (15.5)
	Ex-smoker	1074 (46)	2297 (45.8)	309 (46)	532 (44.8)	1012 (46)	2102 (47.4)
	Missing category	<5	12 (0.2)	<5	N<5	<5	N<5
Ethnicity	**White**	977 (41)	2052 (41.5)	286 (43)	500 (42.1)	983 (44)	1944 (43.8)
n (%)	**South Asian**	120 (5)	229 (4.6)	20 (3)	31 (2.6)	66 (3)	146 (3.3)
	Black	62 (3)	122 (2.4)	<5	9 (0.8)	31 (1)	61 (1.4)
	Other	35 (1)	59 (1.2)	<5	5 (0.4)	10 (0)	26 (0.6)
	Mixed	9 (0)	14 (0.3)	<5	N<5	6 (0)	16 (0.4)
	Missing category	1155 (49)	2534 (50.6)	358 (53)	640 (53.9)	1114 (50)	2241 (50.5)
Year starting	**2014**	897 (38)	2090 (41.7)	122 (18)	217 (18.3)	617 (28)	1390 (31.3)
follow-up	**2015**	761 (32)	1668 (33.3)	183 (27)	355 (29.9)	658 (30)	1453 (32.8)
n (%)	**2016**	501 (21)	989 (19.7)	231 (34)	444 (37.4)	609 (28)	1207 (27.2)
	2017	199 (8)	263 (5.2)	135 (20)	171 (14.4)	326 (15)	384 (8.7)

Supplementary Table 15: Characteristics for people dropped from the HbA1c sample due to missing baseline values and/or follow-up values. Compared to the study population at baseline for individuals intensifying treatment from metformin monotherapy with SU, SGLT2i or DPP4i between 2014-2017 (Table 1)

	Category	SU	SU Original cohort	SGLT2i	SGLT2i original cohort	DPP4i	DPP4i original cohort
Counts		1870	5,010	423	1,187	1751	4,434
Age at baseline	**Years**	61.2 (13.2)	61 (13)	56.3 (10.1)	55 (10)	61.6 (12.8)	61 (12)
BMI baseline	**kg/m2**	31.6 (5.6)	32 (6)	36.4 (7.3)	37 (7)	32.8 (6.0)	33 (7)
eGFR baseline	**ml/min/1.73m2**	88.4 (15.1)	89 (18)	95.2 (10.2)	96 (13)	87.6 (15.2)	88 (18)
Systolic BP at baseline	**mmHg**	133.7 (11.8)	133 (14)	134.5 (10.2)	134 (14)	134 (11.5)	133 (14)
HbA1c at baseline	**mmol/mol**	80.1 (16.6)	80 (21)	76.3 (13.2)	77 (17)	73.2 (13.5)	73 (16)
Time taking metformin prior to intensification	**Month**	39.3 (36.4)	40 (37)	37 (32.2)	36 (33)	46.3 (38.4)	44 (37)
Gender	**Female, n (%)**	746 (40)	1988 (39.7)	160 (38)	474 (39.9)	660 (38)	1745 (39.4)
Diagnosis of CVD	**n (%)**	267 (14)	707 (14.1)	46 (11)	119 (10)	231 (13)	601 (13.6)
Diagnosis of HF	**n (%)**	94 (5)	194 (3.9)	8 (2)	24 (2)	71 (4)	146 (3.3)
Diagnosis of retinopathy	**n (%)**	289 (15)	868 (17.3)	70 (17)	181 (15.2)	342 (20)	861 (19.4)
Prescription for ARB or ACE inhibitor	**n (%)**	1007 (54)	2711 (54.1)	244 (58)	670 (56.4)	983 (56)	2490 (56.2)
Prescription for statin	**n (%)**	1275 (68)	3530 (70.5)	292 (69)	819 (69)	1293 (74)	3387 (76.4)
Patient-level index of multiple deprivation	**1 LEAST deprived**	179 (10)	467 (9.3)	31 (7)	93 (7.8)	156 (9)	398 (9.0)
	2	215 (11)	485 (9.7)	38 (9)	99 (8.3)	159 (9)	378 (8.5)
	3	216 (12)	567 (11.3)	43 (10)	117 (9.9)	178 (10)	449 (10.1)
	4	252 (13)	643 (12.8)	39 (9)	99 (8.3)	178 (10)	427 (9.6)
	5 MOST deprived	238 (13)	589 (11.8)	33 (8)	81 (6.8)	206 (12)	479 (10.8)
	Missing category	770 (41)	2259 (45.1)	239 (57)	698 (58.8)	874 (50)	2303 (51.9)
Smoking status	**Non-smoker**	698 (37)	1883 (37.6)	168 (40)	462 (38.9)	639 (36)	1642 (37.0)
	Current	309 (17)	818 (16.3)	76 (18)	193 (16.3)	280 (16)	688 (15.5)
	Ex-smoker	855 (46)	2297 (45.8)	179 (42)	532 (44.8)	832 (48)	2102 (47.4)
	Missing category	8 (0)	12 (0.2)	<5	N<5	<5	N<5
Ethnicity	**White**	714 (38)	2052 (41.5)	179 (42)	500 (42.1)	774 (44)	1944 (43.8)
n (%)	**South Asian**	95 (5)	229 (4.6)	12 (3)	31 (2.6)	64 (4)	146 (3.3)
	Black	56 (3)	122 (2.4)	<5	9 (0.8)	32 (2)	61 (1.4)
	Other	31 (2)	59 (1.2)	<5	5 (0.4)	16 (1)	26 (0.6)
	Mixed	<5	14 (0.3)	<5	N<5	9 (1)	16 (0.4)
	Missing category	969 (52)	2534 (50.6)	226 (53)	640 (53.9)	856 (49)	2241 (50.5)
Year starting	**2014**	668 (36)	2090 (41.7)	49 (12)	217 (18.3)	400 (23)	1390 (31.3)
follow-up	**2015**	563 (30)	1668 (33.3)	92 (22)	355 (29.9)	491 (28)	1453 (32.8)
n (%)	**2016**	440 (24)	989 (19.7)	152 (36)	444 (37.4)	538 (31)	1207 (27.2)
	2017	199 (11)	263 (5.2)	130 (31)	171 (14.4)	322 (18)	384 (8.7)

Supplementary Table 16: Characteristics for people dropped from the BMI sample due to missing baseline values and/or follow-up values. Compared to the study population at baseline for individuals intensifying treatment from metformin monotherapy with SU, SGLT2i or DPP4i between 2014-2017 (Table 1)

	Category	SU	SU Original cohort	SGLT2i	SGLT2i original cohort	DPP4i	DPP4i original cohort
Counts		1128	5,010	363	1,187	1182	4,434
Age at baseline	**Years**	59.4 (13.0)	61 (13)	55.1 (10.0)	55 (10)	60.3 (12.6)	61 (12)
BMI baseline	**kg/m²**	31.8 (6.1)	32 (6)	36.5 (7.7)	37 (7)	33 (6.4)	33 (7)
eGFR baseline	**ml/min/1.73m²**	90 (14.5)	89 (18)	96 (10.3)	96 (13)	88.6 (14.8)	88 (18)
Systolic BP at baseline	**mmHg**	132.2 (6.5)	133 (14)	133.5 (5.4)	134 (14)	132.3 (6.6)	133 (14)
HbA1c at baseline	**mmol/mol**	80.9 (17.1)	80 (21)	77.6 (13.5)	77 (17)	73.9 (14.1)	73 (16)
Time taking metformin prior to intensification	**Month**	39.1 (35.9)	40 (37)	38.7 (34.7)	36 (33)	45.5 (39.0)	44 (37)
Gender	**Female, n (%)**	422 (37)	1988 (39.7)	142 (39)	474 (39.9)	473 (40)	1745 (39.4)
Diagnosis of CVD	**n (%)**	146 (13)	707 (14.1)	36 (10)	119 (10)	147 (12)	601 (13.6)
Diagnosis of HF	**n (%)**	46 (4)	194 (3.9)	<5	24 (2)	39 (3)	146 (3.3)
Diagnosis of retinopathy	**n (%)**	159 (14)	868 (17.3)	60 (17)	181 (15.2)	213 (18)	861 (19.4)
Prescription for ARB or ACE inhibitor	**n (%)**	549 (49)	2711 (54.1)	191 (53)	670 (56.4)	615 (52)	2490 (56.2)
Prescription for statin	**n (%)**	759 (67)	3530 (70.5)	251 (69)	819 (69)	855 (72)	3387 (76.4)
Patient-level index of multiple deprivation	**1 LEAST deprived**	106 (9)	467 (9.3)	25 (7)	93 (7.8)	103 (9)	398 (9.0)
	2	137 (12)	485 (9.7)	39 (11)	99 (8.3)	108 (9)	378 (8.5)
	3	127 (11)	567 (11.3)	31 (9)	117 (9.9)	132 (11)	449 (10.1)
	4	154 (14)	643 (12.8)	37 (10)	99 (8.3)	120 (10)	427 (9.6)
	5 MOST deprived	133 (12)	589 (11.8)	26 (7)	81 (6.8)	147 (12)	479 (10.8)
	Missing category	471 (42)	2259 (45.1)	205 (56)	698 (58.8)	572 (48)	2303 (51.9)
Smoking status	**Non-smoker**	408 (36)	1883 (37.6)	136 (37)	462 (38.9)	452 (38)	1642 (37.0)
	Current	214 (19)	818 (16.3)	67 (18)	193 (16.3)	193 (16)	688 (15.5)
	Ex-smoker	498 (44)	2297 (45.8)	160 (44)	532 (44.8)	536 (45)	2102 (47.4)
	Missing category	8 (1)	12 (0.2)	<5	N<5	<5	N<5
Ethnicity	**White**	443 (39)	2052 (41.5)	171 (47)	500 (42.1)	531 (45)	1944 (43.8)
n (%)	**South Asian**	53 (5)	229 (4.6)	12 (3)	31 (2.6)	33 (3)	146 (3.3)
	Black	32 (3)	122 (2.4)	<5	9 (0.8)	23 (2)	61 (1.4)
	Other	18 (2)	59 (1.2)	<5	5 (0.4)	12 (1)	26 (0.6)
	Mixed	<5	14 (0.3)	<5	N<5	<5	16 (0.4)
	Missing category	578 (51)	2534 (50.6)	178 (49)	640 (53.9)	578 (49)	2241 (50.5)
Year starting	**2014**	386 (34)	2090 (41.7)	43 (12)	217 (18.3)	238 (20)	1390 (31.3)
follow-up	**2015**	321 (28)	1668 (33.3)	78 (21)	355 (29.9)	318 (27)	1453 (32.8)
n (%)	**2016**	267 (24)	989 (19.7)	126 (35)	444 (37.4)	355 (30)	1207 (27.2)
	2017	154 (14)	263 (5.2)	116 (32)	171 (14.4)	271 (23)	384 (8.7)

Supplementary Table 17: Characteristics for people dropped from the systolic blood pressure sample due to missing baseline values and/or follow-up values. Compared to the study population at baseline for individuals intensifying treatment from metformin monotherapy with SU, SGLT2i or DPP4i between 2014-2017 (Table 1)

9.5.2 Excerpt from ISAC application

PROTOCOL NUMBER: 16_267

I. Sample size considerations

A recent study using CPRD data comparing people on antidiabetic therapies for T2DM reported a mean follow-up time of 2.8years, after initiating treatment with metformin and sulfonylurea dual therapy.(160) We will assume that the follow-up time will be similar in this study, which is a cautious estimate as the study censored participants at the point of further switching. A study by Hung et al, 2012 that described persistent (confirmed 3-12 months after) falls in eGFR of 25%, or ESRD as the composite end point, in a cohort of people with T2DM selected from veterans' health records, this is a similar outcome to our primary outcome of interest.(158) They reported annual rates of the composite end point to be between 3.2% and 5%.(158). This study has a tighter outcome definition than we plan for our primary analysis, as we do not require persistent falls in eGFR. However, assuming a similar 3% outcome rate, the results displayed in Table 9.1 shows the minimal effect size for each exposure group that we could detect with an 80% power.(166) Our study would be adequately powered to detect clinically relevant differences in effect.

Exposure group vs. MTF+SU (n=54,288)	**Estimated smallest HR detected with 80% power**
MTF + DPP4i (n=16386)	0.88 or 1.12
MTF + TZD (n= 10115)	0.86 or 1.14
MTF + SGLT2i (n=1314)	0.68 or 1.36
Assuming 3% outcome rate in baseline group over a 3 year follow-up period. Two-sided significance level of 95%	

Table 9.1 Power considerations for composite endpoint (first occurrence of a decrease of 50% or more in eGFR, or end-stage renal disease or renal replacement therapy) in dual users: using Cox regression command in Stata